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STEREOELECTRONIC EFFECTS IN GENERAL BASE CATALYSIS BY CARBOXYLATE. THEORETICAL CALCULATIONS AND STUDIES IN THE SYNTHESIS OF NEW INTRAMOLECULAR MODELS OF ENZYMATIC CATALYSIS

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STEREOELECTRONIC EFFECTS IN GENERAL BASE CATALYSIS BY CARBOXYLATE. THEORETICAL CALCULATIONS AND STUDIES IN THE SYNTHESIS OF NEW INTRAMOLECULAR MODELS OF ENZYMATIC CATALYSIS.

A Dissertation

Submitted to the Graduate Faculty of the
Louisiana State University and
Agricultural and Mechanical College
in partial fulfillment of the
requirements for the degree of
Doctor in Philosophy

in

The Department of Chemistry

by
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B.S., Instituto Tecnologico y de Estudios
Superiores de Monterrey, 1977
December, 1984

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I would like to express my gratitude to my wife, Patricia, for her endless patience, unconditional love, understanding, and cheerfulness. Also to my parents, for their support and inspiration, I am eternally grateful.

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ABSTRACT.

The hypothesis of the existence of stereoelectronic effects in the reactions in which carboxylate acts as a general base catalyst is further studied through the use of theoretical methods. *Ab initio* calculations on the structures and relative energies of the syn and anti conformations of formic acid at different degrees of solvation are described. These calculations indicate that the syn conformation is more stable in aqueous phase than the anti by 11.9 (at the STO-3G//STO-3G level), 6.9 (4-31G//4-31G), and 2.5 kcal/mol (6-31G**//4-31G). This last number, though, comes from single point calculations at the 6-31G** level on the 4-31G optimized structure and is not consistent with the trends observed with the other basis sets. The greater stability of the syn conformation of carboxylic acids in aqueous solution should cause the higher basicity of carboxylate ion when acting as a base in the syn orientation.

In order to experimentally test this hypothesis, an intramolecular model of ester hydrolysis reactions with a syn-oriented carboxylate is designed and progress towards its synthesis is described. To test the more critical reactions in the synthetic scheme, a series of stilbene-containing cyclic ethers is synthesized through the use of a novel etherification procedure in mixed solvents in very high

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yields, followed by a low-valent titanium induced coupling of *bis*(carbonyl) compounds. Overall yields of 61 to 74 % for the two-step conversions are obtained. The crystal structures by X-ray diffraction of some of these new compounds are determined and described.

To extend the synthetic sequence described above to functionalized stilbenes, a large number of 2,6-disubstituted benzaldehydes with various protecting groups are prepared and their selective deprotections investigated. Several *bis*(aryl) ethers are prepared using the etherification reaction used for the cyclic stilbenes and transformed into *bis*(benzaldehyde) compounds containing protected functional groups by dilithiation, followed by reaction with *N,N*-dimethylformamide. All attempts to form stilbenes from these compounds by reaction with low-valent titanium result in decomposition. Alternative preparations, both short and highly probable, of the desired models from the intermediates already synthesized are suggested.

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INTRODUCTION.

Enzymes are some of the most efficient catalysts known to man, with rate enhancements on the order of 10^{10} to 10^{14}. The detailed knowledge of their mechanism and the factors to which they owe such efficiencies is therefore of interest not only from the phenomenologic, but also from the practical point of view, since the knowledge of the different mechanisms of rate enhancement used by enzymes should enable the chemist to build better and more efficient synthetic catalysts.

A very significant portion of the present knowledge on the chemistry of enzymatic catalysis comes from the studies of intramolecular models. These models are smaller, more accesible molecules that mimic some of the features of the enzymatic reaction by holding the substrate and catalyzing groups in close proximity, thereby resembling the enzyme-substrate complex.

According to Gandour,[1] intramolecular models can be classified as mimetic models, which model specific enzymes, and nonmimetic models, which model a specific feature of the general process of enzymatic catalysis. Most of the recent research in the latter area is concentrated in the effects of complexations by cyclodextrins,[2] cavitands,[3] and "octopus" type hosts.[4]

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The work described in this dissertation is part of an ongoing program to synthesize nonmimetic models of enzymatic catalysis which model a common chemical event in enzymic reactions, general base catalysis. In particular, the ultimate goal of this research is the understanding of the effects of the relative orientation of a carboxylate anion when acting as a general base.

This dissertation is divided in four chapters. Chapter I gives the necessary background information and describes the design of the intramolecular model chosen. Chapter II describes the use and results of theoretical calculations as applied to this problem. The use of simpler, more synthetically accessible molecules to test the more critical reactions in the synthetic pathway to our desired model are given in Chapter III. Finally, Chapter IV describes the efforts and progress in the preparation of the synthetic model of enzymatic catalysis.

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CHAPTER I. Catalysis by Enzymes and Intramolecular Models. Design of a New Intramolecular Model of General Base Catalysis by Carboxylate.

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I.1 Enzymatic Catalysis and Intramolecular Models. Enzymes are known to be some of the most efficient catalysts for a wide range of different chemical reactions, with rate accelerations of the order of 10^{10}-10^{14} over the non-catalyzed reactions. Although the detailed mechanisms and the relative importance of the different factors to which they owe their efficiency is still under debate, the mode of action of a large number of enzymes has been established.

Currently, most researchers in the field agree that the principal factors responsible for enzymatic catalysis[5] are as follows:

complexation,
chemical catalysis by neighboring groups,
collection of reactants, and
orientation.

The quantification of the extent to which each of these factors contribute to the overall catalytic activity of the enzymes has been a long sought goal in this field[6] of research. However, even when considerably progress has been made largely through the study of intramolecular models,[7] no agreement on reasonable partitions of the overall rate accelerations found in enzymatic reactions has been reached.

a) Complexation. The binding of the substrate by the enzyme is the first event in any enzymatic reaction, and undoubtly a very important factor in the large specificities exhibited by them. It has been long recognized[8,9] that the most favor-

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able complexation should take place at the transition state level, rather than at the reactant state. A stabilization of the latter, without a larger decrease of the energy of the complexed transition state, would lead to a higher energy barrier and hence to inhibition rather than catalysis. This view has found extensive support in the successful use of transition state analogues as inhibitors of enzymes.[10,11]

More recently, it has been proposed[12] that all the catalytic efficacy of enzymes is due to stabilization of the transition structure. This proposal is mainly a rewording of all the previous explanations of enzyme activity in terms of the changes in enthalpy and entropy of the transition state. Although this seems a natural and thermodynamically more sound approach to explain the different factors involved in enzymatic catalysis, this discussion is made in terms of the different effects already proposed to be consistent with the majority of the published literature.

b) Chemical catalysis. Once a substrate is bound to the active site of an enzyme, it is set into a location in which several functional groups from the different aminoacid side chains can be advantageously utilized to catalyze the reaction.[13] The most common of these are the carboxylate groups in aspartate and glutamate and the imidazole in histidine. At neutral pH the carboxylate anions are fully ionized (pKa = 3.8 and 4.2, respectively), while the imidazole group in in histidine (pKa = 6) exists as the free base in signifi-

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cant concentrations. These functional groups in their respective ionization states can act either as bases or nucleophiles. The thiolate group of cysteine (pKa = 8), the phenoxide form of tyrosine (pKa = 10), and the β-hydroxyl of serine (pKa = 13.7) are also active as nucleophiles. In addition, many enzymes contain metals which can act as electrostatic catalysts to stabilize anions.

The most important mechanisms of chemical catalysis

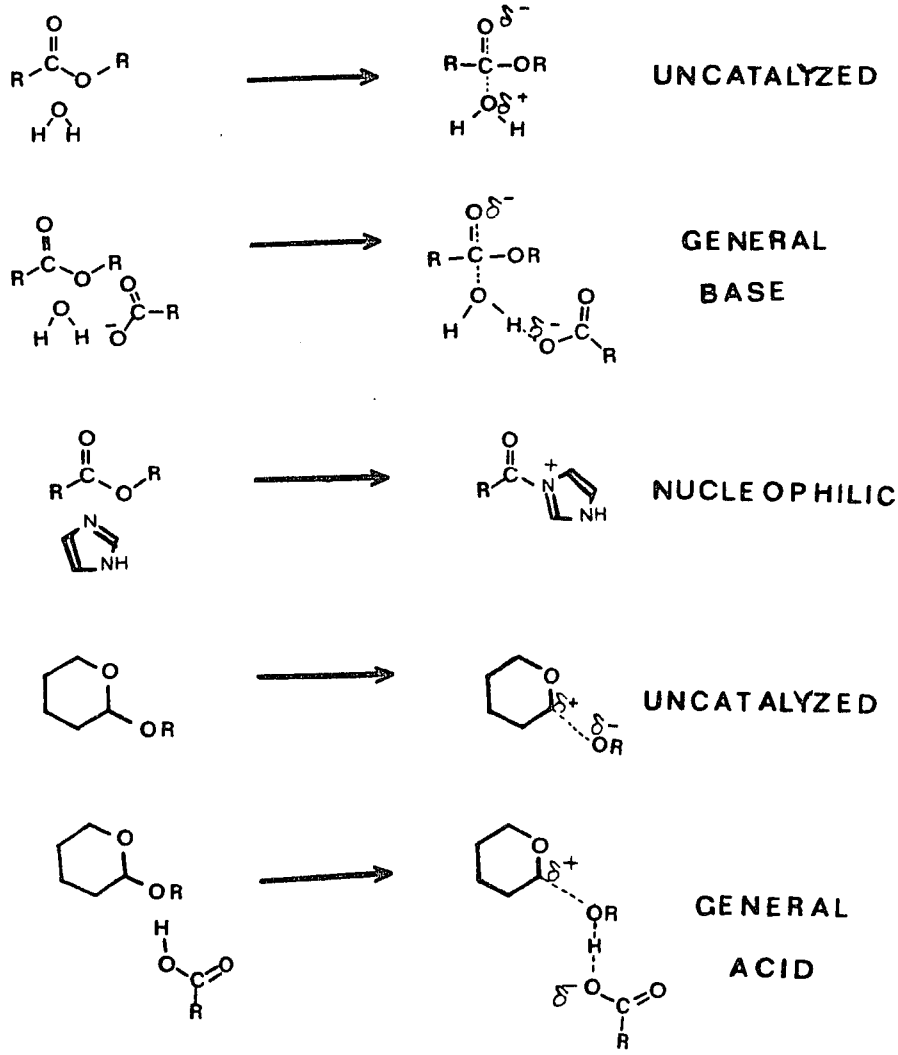

Figure 1. Important mechanisms of chemical catalysis by functional groups in enzymes.

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proposed in enzymic activity are compared to their non-catalytic counterparts in Figure 1. In the uncatalysed hydrolysis of an ester, or amide in the case of proteases, the nucleophilic attack of water to the carbonyl carbon leads to the development of a partial positive charge on the water oxygen and a partial negative charge in the carbonyl oxygen on the transition structure. This increase of charges leads to relatively unstable transition structures, with the concomitant high energies and low rates of reaction. The dispersion of this excessive charge through the donation of a proton to an anion (acid catalysis) or the abstraction of a proton from a cation (base catalysis) leads to more stable transition structures and faster rates of reaction.

For the hydrolysis of esters two different mechanisms of catalysis are possible with the functional groups available in enzymes. In the first case a carboxylate acts as a general base, hence the name of general base catalysis, accepting a proton from the water molecule leading to a better dispersion of the charge which lowers the energy of the transition structure thereby causing an increase in the rate. The second possibility is illustrated by the use of an alternative nucleophile, imidazole in the example provided here, which leads to a highly reactive intermediate which can be easily hydrolyzed. This mechanism is called nucleophilic catalysis. It is also called covalent catalysis in the older literature.

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In the case of the hydrolysis of acetals, the spontaneous scission of one of the C-O bonds leads to a transition structure which is structurally close to an oxocarbonium ion (which is known to be a relatively stable ion) and an alkoxide. In the general acid catalysis example a molecule of a carboxylic acid donates a proton to this alkoxide, thereby generating a more disperse charge distribution which lowers the energy and accelerates the reaction.

Metal ions have been proposed to catalyse the hydrolysis of amides through electrostatic stabilization of the developing negative charge in the carbonyl oxygen in the transition structures.

The quantification of the effect of this chemical catalysis in enzymes is not readily attainable, and is in this area that the use of intramolecular models as enzyme mimics first gained widespread acceptance. The principle behind their utilization lies in the fact that, on attaching both the substrate and the catalyst functionalities to the same molecular framework an analog to the enzyme-substrate complex is preformed. This facilitates the study of the subsequent reaction and, if necessary, makes the chemical modifications much simpler than in the enzyme itself.

The use of intramolecular models introduces some other advantages. The relative orientation of the reacting groups is fixed by the framework to which they are attached, thereby making the separation of orientation effects and

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intrinsic catalytic effects (at least in principle) accessible by variations of the molecular skeleton. The direct comparison of the unimolecular rate constants in models (in units of s^{-1}) to the bimolecular counterparts (in $l\ mol^{-1}s^{-1}$) is not possible. However, the quotient of these rate constants does give a value in units of mols. This quotient is normally referred to as the "effective molarity" (EM) and has been widely utilized to assess the effectiveness of the catalytic group under study.[14]

The main disadvantage of intramolecular models is that, since the ground state of the new reaction has the reacting groups already juxtaposed, any effects that in the enzymatic reaction could be attributed to the collection of reactants is superimposed to the catalytic acceleration caused by the added functional group. Due to this problem, the separation of rate enhancements due to collection of reactants or chemical catalysis is impossible to attain through the study of intramolecular models.

The mechanistic studies done in the last decades on intramolecular catalysis have played a very important role in the elucidation of the chemistry of the functional groups involved in enzyme catalysis. Not surprisingly, most efforts have been concentrated in the study of nucleophilic, general acid, and general base catalysis. Several examples of intramolecular models[14] for catalysis and their effective molarities are illustrated in Figure 2. From the data presented on

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this figure it can be clearly seen that the nucleophilic catalysis models show considerably larger rate enhancements than the either of the protolytic models. The range of effective molarities for nucleophilic catalysis spans from 10^4 to 10^8 M, while general acid catalysis mechanisms provide accelerations up to 10^4. General base catalysis show much smaller enhancements, with values up to 80 M, than either nucleophilic or general acid catalysis models.

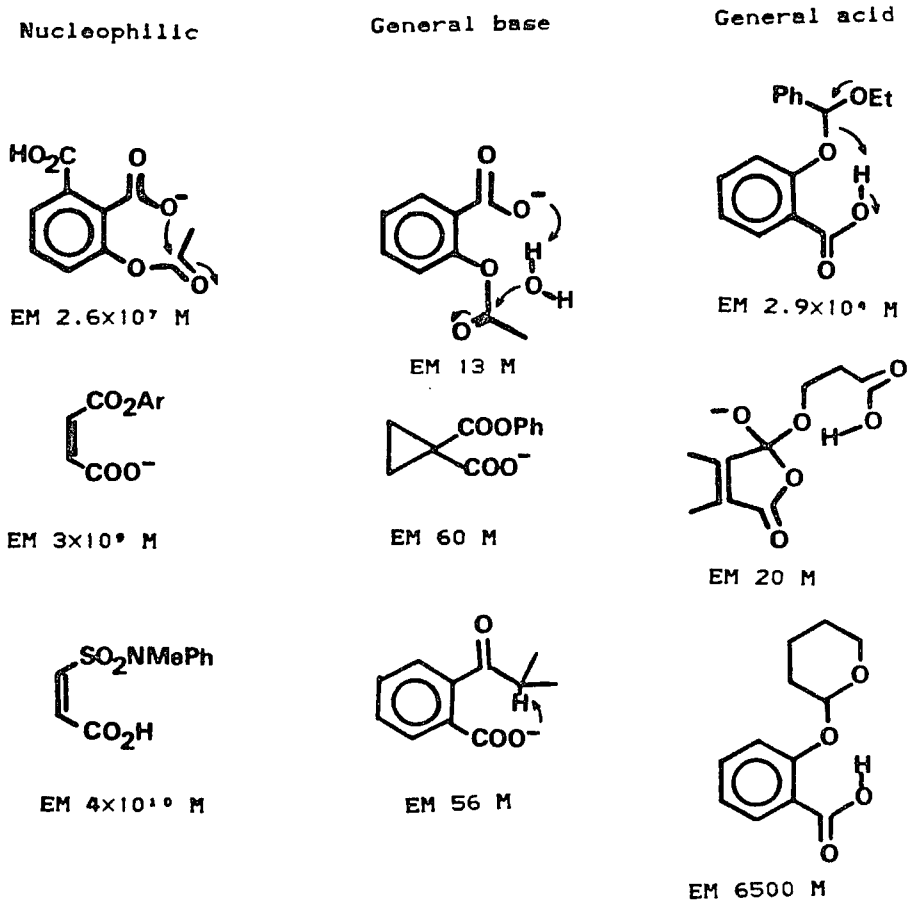

Figure 2. Some intramolecular models of catalysis.

This large difference in effectivities between nucleophilic and general acid-base catalysis has been attributed

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to a lower entropic gain because of the formation of "very loose" (low vibrational frequencies) bonds to hydrogen in the protolytic mechanisms.[15] The generality of the low effective molarities in general base catalysis prompted Kirby[16] to express that either all the intramolecular models tested possessed common characteristics that hindered their reactivities, or the general acid-base catalysis was an inherently poor mechanism of rate acceleration. He supported the latter theory and stated in a later review[14] that as a rule "... if the effective molarity is greater than 80 M the mechanism is nucleophilic. If it is less than 80 M is almost certainly general acid or general base catalysis." c) Collection of reactants. From studies of these and other intramolecular models of enzymic activity the general consent was that most of the rate accelerations found were due to the loss in entropy on going from an intermolecular reaction, in which at least two molecules have to come together to form a single species (product or transition structure), to an intramolecular model in which a single molecule reacts with itself. In particular, Bruice et al[17] proposed that the loss in translational entropy was enough to cause the rate accelerations. Bruice and Benkovic[18] later observed that for many reactions $T\Delta S\ddagger$ decreases by 5 kcal/mol in adding one molecule to the transition state.

From simple statistical mechanic calculations (rigid rotor, harmonic oscillator, Sackur-Tetrode equation) Page

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and Jencks[19] proposed that the entropy loss due to the conversion from a bimolecular to an intramolecular reaction could be accounted for in the following manner :

Breakdown of Entropy Factors

3 translational degrees of freedom (MW=20-200)		28-35 eu ($cal\text{-}K^{-1}mol^{-1}$)
3 rotational degrees of freedom		21.5 eu
internal rotations		3.1-5.0 eu
vibrations	(1000 cm^{-1})	0.1 eu
	(800 cm^{-1})	0.2 eu
	(400 cm^{-1})	1.0 eu
	(200 cm^{-1})	2.2 eu
	(100 cm^{-1})	3.4 eu

The entropy for the internal rotations used was the average entropy change per degree of rotational freedom lost in cyclizations of hydrocarbons, approximately 5 eu. These data were reviewed more recently by Jencks.[20] In this paper he termed the entropic gain the "Circe Effect". Since all the calculations from which the data was drawn were based on gas phase, he added an empirical correction for solvation of 5 eu. This correction brought the total entropy difference to -35 eu, which can be translated to a ΔG of 10.5 kcal/mol, a rate factor of 10^8 M according to absolute rate theory. From this total factor he ascribed 10^3 M to loss of rotational freedom, and from 10^3 to 10^5 M to the effects of catalytic groups.

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In a recent review of data, Bruice[21] restated that most of the rate acceleration could be explained by the loss of translational entropy in bringing the substrates together. He proposed the name of "Propinquity" for this effect, which he called "the common sense phenomenon", and added that holding the reacting groups in the proper orientation would bring an additional entropic advantage. He estimated that both combined effects could account for up to 35 eu (a factor of 10^8 M at 25°C). This proposal was further supported by the fact that several solvent-independent bimolecular reactions (i.e. Diels-Alder) showed $\Delta S\ddagger$ of -30 to -45 eu.

A separate estimate of the entropy effects[22] which utilized a spherical geometry approach to estimate orientation effects coupled with statistical mechanics gave values of up to 1809 M for the accelerations.

d) Orientation. The more controversial issues in this field of research have arisen on attempts to quantify the effect of geometric orientation of the different reacting groups on the overall rate acceleration. One of the first assignments of a rate acceleration due exclusively to orientations was the "Stereopopulation Control" theory developed by Cohen and coworkers.[23],[24] They postulated, based on the large rate differences (up to a factor of 3×10^{11}) caused by methyl substitutions on the lactonization of dihydrocoumarinic acid[23] and cyclizations of the alcohols (up to 9×10^5) derived from them by reduction[24], that a "trimethyl lock" would cause a

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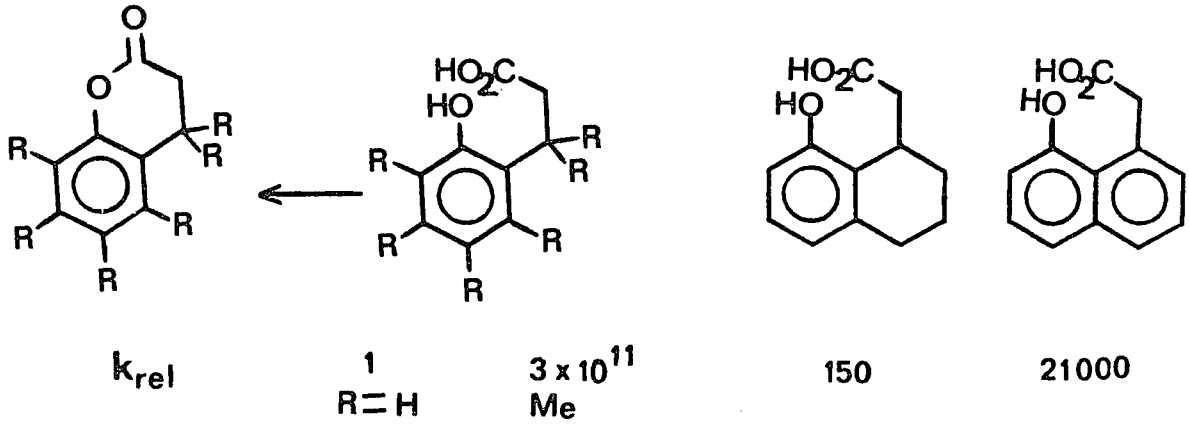
higher population of the conformation required for the closing of the cycle thereby accelerating the reaction. Additional supporting data came from the studies of the lactonizations of coumarinic acids.[25] In this case, the system was already constrained to the orientation favorable to cyclization, and methyl substitution should decrease the rate. The experimentally observed effect was a decrease of 10^3 in rate.



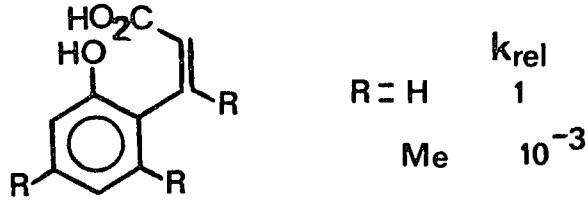


Figure 3. Relative rates of lactonizations.

This proposal was not very well accepted. Although the principle was agreed upon, the magnitude of the effects proposed by Cohen were severely criticized. The main criticisms to it were based on the fact that large amounts of ground

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state strain were impossed on the model system by methyl substitution. X-Ray diffraction studies showed large distorsions on the compounds utilized by Cohen.[26] The comparison in rates between the naphthalene and tetraline compounds shown in Figure 3, in which the steric and strain factors should be very similar showed rate enhancements of only 140.[27] Force field calculations revealed that up to 10^3 M could be explained exclusively from ground state strain relief.[28] This ground state strain is not likely to play any role in enzymatic catalysis, since enzymes have rather flexible structures. In crystallographic studies it has been observed that enzymes distort on binding of small molecules rather than the converse.[29] This was, as a matter of fact, a supporting argument from proponents of the "Induced Fit Model".[30]

Another hypothesis on the effect of orientations was the "Orbital Steering" theory proposed by Koshland.[31] Based on the rates of cyclization of several bicyclic hydroxy acids and their thiol analogues, he proposed that in an optimal case, the reacting groups should follow a path dictated by the spatial requirements of the orbitals involved in the reaction. Furthermore, he postulated that a deviation of 10° from the optimal path could cost up to a factor of 10^4 M in the rate acceleration. In his analysis of the rate data, the only correction he used for the effect of proximity is 55.5 M (the concentration of water).

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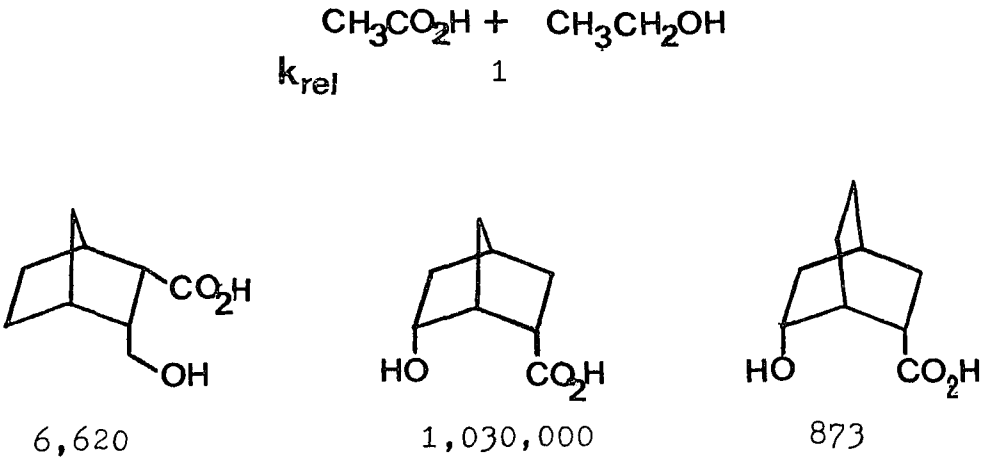

Figure 4. Relative rates of lactonization in bicyclic compounds.

This proposal has been severely criticized on different grounds.[32] Several of the structures of his models had been incorrectly assigned,[33] the existence of a change in the rate determining step in one of the reactions,[34] force-field calculations showed that steric effects could account for the whole rate acceleration,[35] deficiencies on the model used for entropy loss,[36] and Koshland's choice of corrections for proximity effects.[37] A posterior analysis of Koshland's data[7] showed that a logarithmic plot of the rate constants vs. the equilibrium constants gave straight lines with slopes of 0.9 and 0.7 for the formation of lactones and thiolactones, except for one compound, which cyclized faster by a factor of 10^2 on the basis of that correlation. It was proposed that this might be the real factor to be gained by

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the orientation, while the remaining observed accelerations could be explained on the basis of equilibrium arguments.

Theoretical calculations on simpler models to study this effect were contradictory. When optimization of structure on simple models was done, values much lower than those predicted by Koshland were found. Calculation at the EHT level on the addition of water to formaldehyde showed effects that were at least one order of magnitude lower.[38] CNDO/2 calculations showed that a very shallow potential well represented the deviation from the "optimal" approach.[39] The *ab initio* calculations by Burgi, Lehn, and Wipff[40] on the addition of hydride to formaldehyde showed that at a distance of 2.5 A (the calculated hydride to carbon distance for the transition structure), a 20° lateral deviation costed only 2 kcal/mol (30 M). PRDDO calculations showed favorable interactions in a cone that spanned a solid angle of 35°. The calculated force constant at this level for the bending of the nucleophile to carbonyl carbon bond was only 0.062 kcal/mol-degree^2, from where an energy increase of only 3.1 kcal/mol (175 M) could be calculated.[41]

In contrast to these results, a CNDO/2 level calculation[42] using the active residues of chymotrypsin at the geometry determined by X-ray diffraction showed that a deviation of 0.2 A (5.75°) caused an energy rise of 0.27 ev, which was equated into a 1.25×10^{-2} relative rate by using an empirical correction factor of 0.43 for the energy differ-

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ence. A deviation of 0.4 Å (11.3°) caused an energy increase of 0.4 ev, equivalent to a 1.97×10^{-4} relative rate.

The criticism to the "Orbital Steering" hypothesis best supported by experimental data was probably the recent report by Menger.[43] In order to avoid the ambiguities on Koshland's models, he chose as a model the direct comparison between pairs of compounds which would have very similar distances between the reacting groups, inherent reactivities of the hydroxyls, steric interactions, and definite measurable angular differences. He proposed for these compounds the name of "reversomers" (see Figure 5). The difference in the

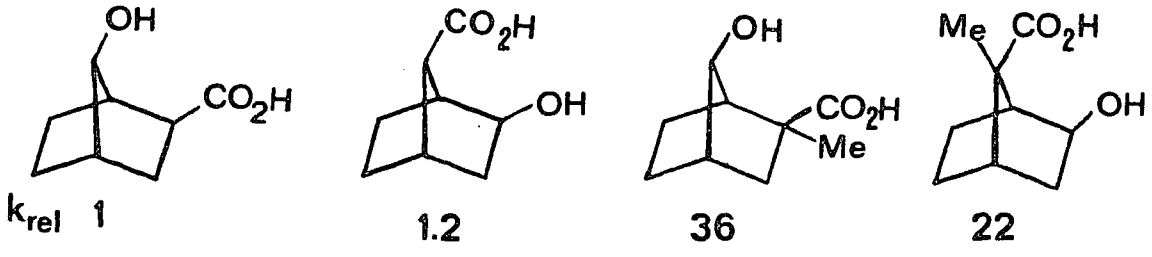

Figure 5. Relative rates of lactonization of "reversomers".

angles of approach was 10° according to molecular mechanics calculations. This difference would give, following the orbital steering hypothesis, a 10^4 rate effect. The experimentally found factors were very small, 1.2 and 1.6. The identity in steric factors between both lactones was determined by molecular mechanic calculations and the IR frequencies of the C=O stretchings. This data and the analysis of

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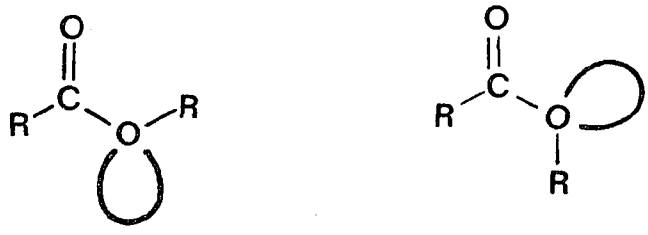
other published material compelled Menger to publish his "cone of trajectories" proposal.[44]

The most recent hypothesis on the effect of orientation in reactivity is the "Stereoelectronic Effect" theory of Deslongchamps.[45] In its simplest expression, the stereoelectronic effect can be illustrated in the structure of carboxylate esters. The two different possible conformations of an



syn anti

Figure 6. Stereoelectronic effects in structure of esters.

ester, normally denoted as *Z*- or syn and *E*- or anti (see Figure 6), have different relative orientations of their orbitals. The favorable interaction between the lone pairs (n) in the oxygen in the syn ester and the antibonding (σ^*) orbital of the carbon to oxygen carbonyl bond, which is absent in the anti conformation has been proposed to be the reason for the greater stability of the syn conformation. This difference in energy due to the stereochemical demands on the electronic structure has been proposed as an explanation for the differences in the observed rates of hydrolysis of acyclic esters (syn) and small ring lactones (anti).[46]

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The stereoelectronic effect has found ample experimental support in its successful utilization, albeit only in a qualitative fashion, to predict the direction of cleavage in tetrahedral intermediates of acyl transfer reactions, the hydrolysis of orthoesters, and as a rationale to the anomeric effect.[47] In contrast, only a very brief speculation of its possible implications in enzymatic catalysis has been published.[47] e) Total rate enhancements. In what is probably the most quoted partition of the total rate acceleration from an enzymatic reaction, Bender[48] proposed the following contributions to the observed rate of the α-chymotrypsin catalyzed hydrolysis of N-acetyltryptophanamide:

Factor	Origin	Effect	Rate constant
-	Estimated rate constant for alkaline hydrolysis		3.0×10^{-4} $M^{-1}s^{-1}$
1	Conversion to imidazole catalysis	1.6×10^{-6}	4.8×10^{-10} $M^{-1}s^{-1}$
2	Intramolecularity	10 M	4.8×10^{-9} s^{-1}
3	Change to an alcoholysis	10^2	4.8×10^{-7} s^{-1}
4	"Freezing" from specificity	10^3	4.8×10^{-4} s^{-1}
5	General acid catalysis	10^2	4.8×10^{-2} s^{-1}
-	Observed rate constant		4.4×10^{-2} s^{-1}

The first two entries in this Table represent the choice of a standard, uncatalyzed reaction, and factors 2

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through 5 are the suggested value for each of the catalytic effects. In this partition, Bender chose to divide the different contributions in a different manner to the one just discussed. The change to alcoholysis (nucleophilic catalysis, factor 3) and general acid catalysis (factor 5) are due to catalysis by functional groups, the intramolecularity factor (2) could be translated to a collection of reactants factor, and the "Freezing" from specificity factor (4) to an orientation effect. Even when the specific values of the orientation and collection effects, according to more recent theories should be redistributed, this "dissection" of the catalytic effects is in remarkable agreement to the current concepts of catalysis twenty years after its publication.

I.2 Stereoelectronic Effect on Carboxyl and Carboxylate. Implications on General Base Catalysis. Recently, Gandour[49] put forth the hypothesis that there is a stereoelectronic effect in the general base catalysis by a carboxylate. When a carboxylate ion accepts a proton, it does generate a carboxyl. This has in principle two stable conformations, syn and anti (see Figure 7). Of these two conformations, the syn is the more stable in gas phase as evidenced by microwave spectroscopy[50] and theoretical calculations.[51] The energy difference between these two conformations has been measured in the gas phase for formic acid, but no measurement of this difference in aqueous solution for formic or any other carboxylic acid is available.

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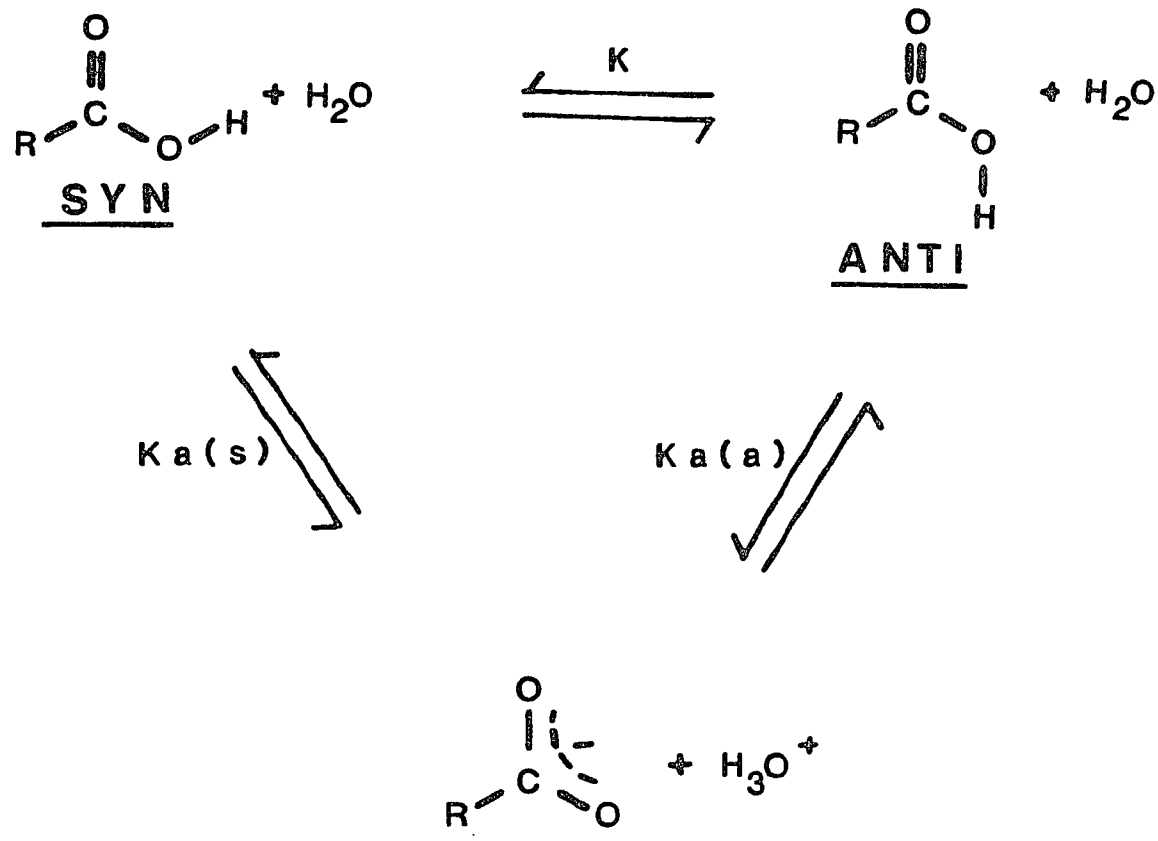

Figure 7. Thermodynamic cycle of ionization of syn and anti carboxylic acids.

Numerous studies[52] of intramolecular general base catalysis by carboxylate have been performed in the past three decades. In all the cases(see Figure 8) the carboxylate is juxtaposed to the reaction center so that the catalyzing proton would be delivered from such a direction as to produce the anti conformer of carboxyl. It is suggested[49] that this orientation results in a loss of effective basicity of the carboxylate and hence a loss in catalytic power.

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The energy difference between the two conformers of carboxyl is likely reflected in the activation barriers of reactions in which a carboxylate acts as a general base catalyst. The extent to which it affects the relative rates

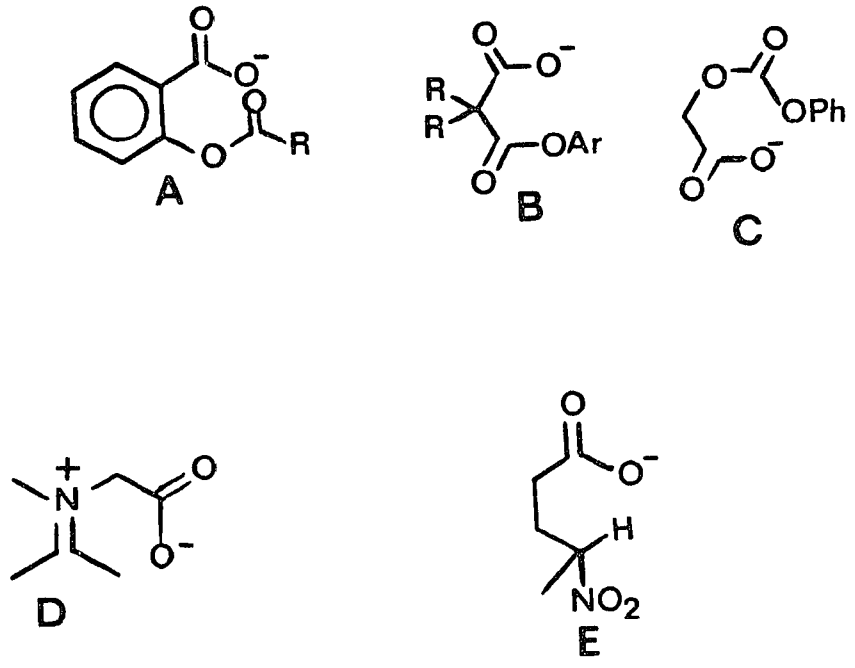

Figure 8. Some models studied in the intramolecular general base catalysis by carboxylate.

can be estimated by use of the Brønsted catalysis law:

$$k=CKa^{-\beta}$$

combination of two similar expressions for syn(s) and anti(a) yields:

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$$[k(s)/k(a)]=[Ka(s)/Ka(a)]^{-\beta}$$

and expressing the ratio of equilibrium constants in terms of Free Energies one finally obtains the following relationship:

$$[k(s)/k(a)]= e^{\beta(\Delta Ga-s/RT)}$$

This last equation relates directly the difference in free energies between the two conformations of the carboxyl and the relative rates expected on reactions subject to general base catalysis by carboxylate in both orientations. In order to estimate the relative rates on the general base catalyzed hydrolyses of esters, the Brønsted β value of this reaction must be known. A value of 0.47 is chosen as a compromise among the measured value of 0.44 in aryl formates,[53] 0.47 in ethyl dichloroacetate,[54] and the estimate of 0.5 (based on the Hammett ρ value) in acetyl salicylic acids by Fersht and Kirby.[55] Substitution of the value for the energy difference determined by Hocking and Bjarnov[50] for formic acid in gas phase (4.09 kcal/mol) gives a relative rate (k(s)/k(a)) of 26.

This obtained value must be taken only as a general guide, since the value utilized for the energy difference comes from its determination in formic acid. Since formic acid is the smallest possible carboxylic acid, it would be reasonable to expect larger energy differences for substi-

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tuted carboxylic acids due to the larger steric interactions of the chains with the proton in the anti orientation. Based on the calculations for acetic and propionic acids Gandour estimated relative rates of $10^{2+-1.49}$ It must be also kept in mind that the measurement of this energy difference is made in gas phase, and solvation effects should have a sizeable effect on the relative energetics in aqueous solution. Nevertheless, this simple approach indicates that there should be a definite rate enhancement on changing the orientation of the carboxylate from anti, which has been used in all models studied to date, to the thermodynamically favored syn.

The orientation hypothesis is also supported by the observation that in all the enzymes whose crystal structures have been solved and which have carboxylates in their active sites, the carboxylates are oriented to interact with the other groups or substrates in a syn manner. The relevant portions of the structures of some of these enzymes are illustrated in Figure 9. For the serine proteases, Kraut[56] has recently discussed the structural features of the carboxylate-imidazole hydrogen bond from the various X-ray studies. The structural features of the acid proteases have been discussed by James.[57]

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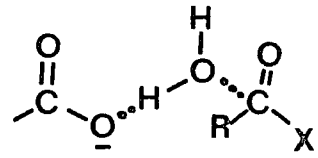
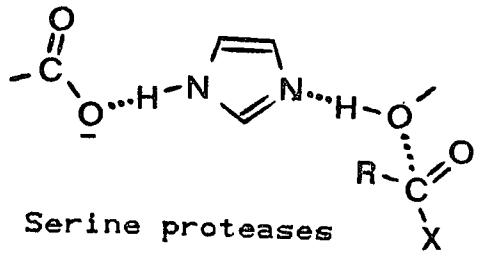
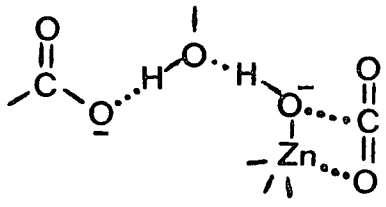


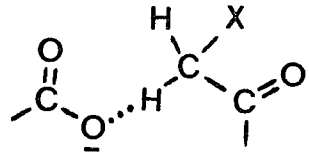
Penicillopepsin



Serine proteases



Carbonic anhydrase B



Glyceraldehyde-3-phosphate isomerase

Figure 9. Partial structures of some carboxylate-containing enzymes as determined by X-ray diffraction.

To test this hypothesis, the design and synthesis of a new intramolecular model of a general base catalyzed reaction are required. Among the reactions in which general base catalysis has been shown to exist, the hydrolysis of esters is the logical choice due to the extensive wealth of data already published on this reaction. The accumulated knowledge on the mechanism of this reaction would makes the comparison and interpretation of results much simpler.

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I.3 Design of a New Model of Intramolecular General Base Catalysis. The design of a molecule which utilizes a carboxylate in the syn orientation as a general base to assist in the hydrolysis of esters has by necessity to be based on a plausible structure for the transition state of this reaction. A transition state, being a local maximum in a potential energy surface, is not a stable species which could be isolated and its structure determined by traditional physical methods. However, some insight into its structure can be gained by kinetic studies and theoretical calculations.

In typical carboxylate general base catalyzed ester hydrolyses, addition of water to the carbonyl carbon to form a tetrahedral intermediate is known to be the rate determining step.[58] Furthermore, it is known that the transition state is a rather late one. This has been determined by Hammett correlations on the phenoxy leaving groups of acetyl salicylic acids[59] (ρ=0.96) and by kinetic isotope effects on their hydrolyses ($k^{12}C/k^{13}C$=1.03).[60] By using the BEBOVIB vibrational analysis program, this kinetic isotope effect has been translated into a 1.78 Å bond length[60] for the nucleophile water oxygen O4 to the carbonyl carbon C5 bond (See Figure 10 for nomenclature). By use of the Pauling's equation,[61] the measured isotope effects for the acetate-catalyzed hydrolysis of aryl acetates[62] have been transformed [7] into a bond length of 1.68 Å for the same O4-C5 bond, and to a C5-O6 bond length of 1.37 Å.

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Additional information on the structure of this transition state was obtained from the theoretical calculations done by Stone and Erskine[63] on addition of nucleophiles to carbonyls. They calculated an angle of 106° for O4-C5-O6,[64] and a O4-C5 bond length of 2.0 Å (this value was not optimized). A hydrogen bond heavy-atom (O2-O4) distance of 2.9 Å was calculated by Umeyama,[65] and agrees with most other calculations on similar systems.[66] The local geometry of the catalyzing carboxylate was based on the calculations by Radom on the formate anion.[67]

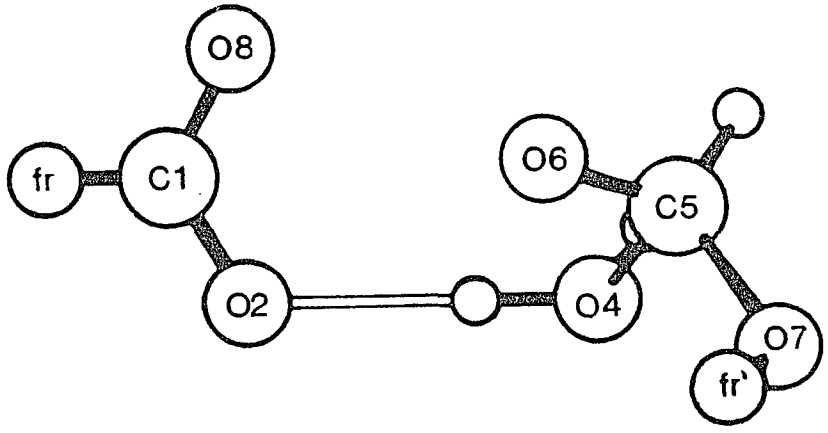

Figure 10. Transition state for carboxylate catalyzed ester hydrolysis. Solid lines represent covalent bonds. Hollow lines represent hydrogen bonds. fr and fr' refer to the points of attachment to a molecular framework.

Combination of all these values rendered the structure depicted in Figure 10. Molecular models of this stucture were built, and different frameworks which would hold the reactant groups in the optimal spacial disposition were built around it.

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The more promising of these models were further studied using the molecular graphics capabilities of the PROPHET system. Among these potential structures, those based on two aromatic rings conected by a two carbon bridge from the positions *ortho* to the functional groups seemed to provide adequate relative orientations of the ester and catalyzing carboxylate in the syn orientation. After both the structures and their relative synthetic accessibilities were considered, the trans-stilbene (1,2-diphenylethene) framework was left as the most accessible synthetic targets. A PROPHET drawing of a transition state based on this structure showing the syn orientation of the carboxylate is shown in Figure 11.

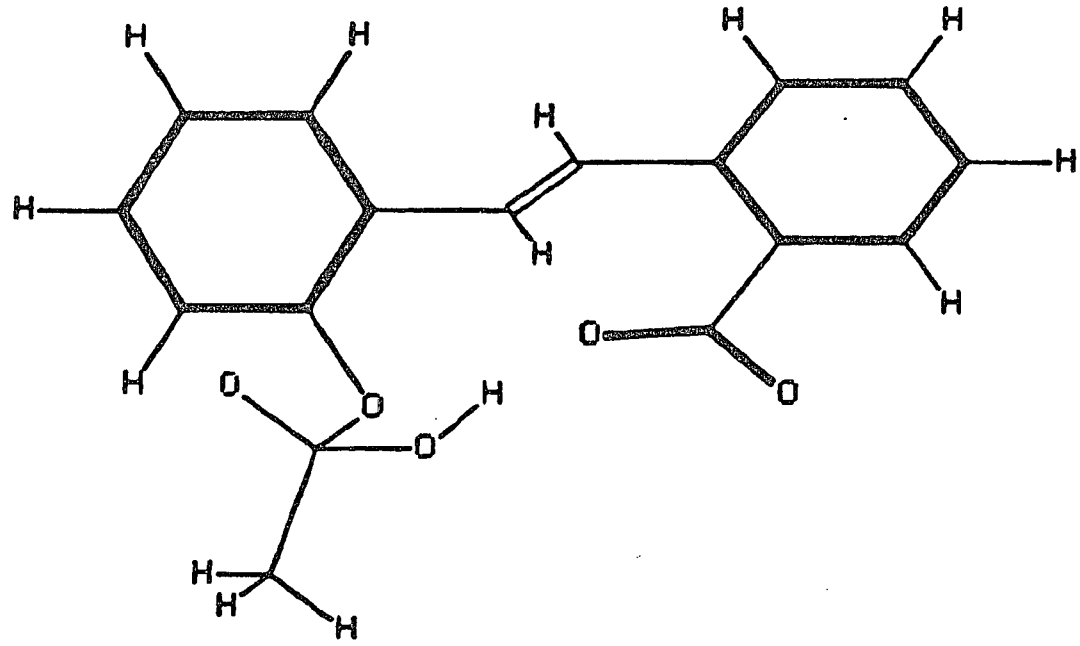

Figure 11. PROPHET Drawing of a possible transition structure for ester hydrolysis in a stilbene model showing the syn orientation of proton transfer to the carboxylate.

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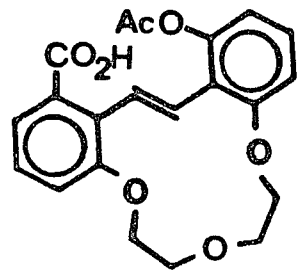
An acyclic stilbenic structure, such as shown in Figure 11 would have the possibility of having both reactant groups on the same side of the plane of the double bond, or on opposite sides, which would render the carboxylate catalytically inactive. From simple steric grounds, the latter conformation should be more stable, and even when an equilibrium between both orientations could be established, the lower population of the catalytically active conformation would produce smaller effects on the overall rate accelerations. In order to avoid this problem, the relative orientation of both aromatic rings has to be held rigid by closing a cycle. A diethylene glycol moiety was chosen for this purpose, producing the structure illustrated in Figure 12 as the primary synthetic goal.



1

Figure 12. Structure of the cyclic stilbene model 1

The sequence chosen for the synthesis of 1 was based on the use of the McMurry[68] low-valent titanium induced reductive coupling of carbonyl compounds to convert the

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dialdehyde 3 into the precursor stilbene 2. This particular reaction was chosen because of its apparent insensitivity to steric hindrance, it has been successfully used to generate highly hindered alkenes,[69] and because of its high tendency to favor intramolecular reactions to form rings in cases where dicarbonyls have been utilized, even in the case of ring sizes which are difficult to form via other routes.[70] However, the nature of the protecting groups that can be used is seriously limited by this reaction. Neither the Oxyphenol Protecting Group, OPG, nor the Carboxylate Protecting Group, CPG, can be esters, since it has been shown[71] that esters react under the conditions of this reaction.

The suitable protected dialdehyde precursor 3 can in principle be synthesized through two different routes. The one illustrated at the left side of Figure 13 represents a classical synthetic approach of generating the two different monoaldehyde intermediates in different reactions, and then forming an ether linkage between them. A possible alternative, sketched in the right side of the scheme, consists of linking both aromatic ring together by forming first the ether bridge, which could then be followed by the introduction of the aldehydic carbonyls.

The synthetic pathway for 3 outlined above, or for that matter any other plausible sequence, has as a crucial step the preparation of 1,2,3-trisubstituted aromatic compounds. The more successful syntheses of these compounds

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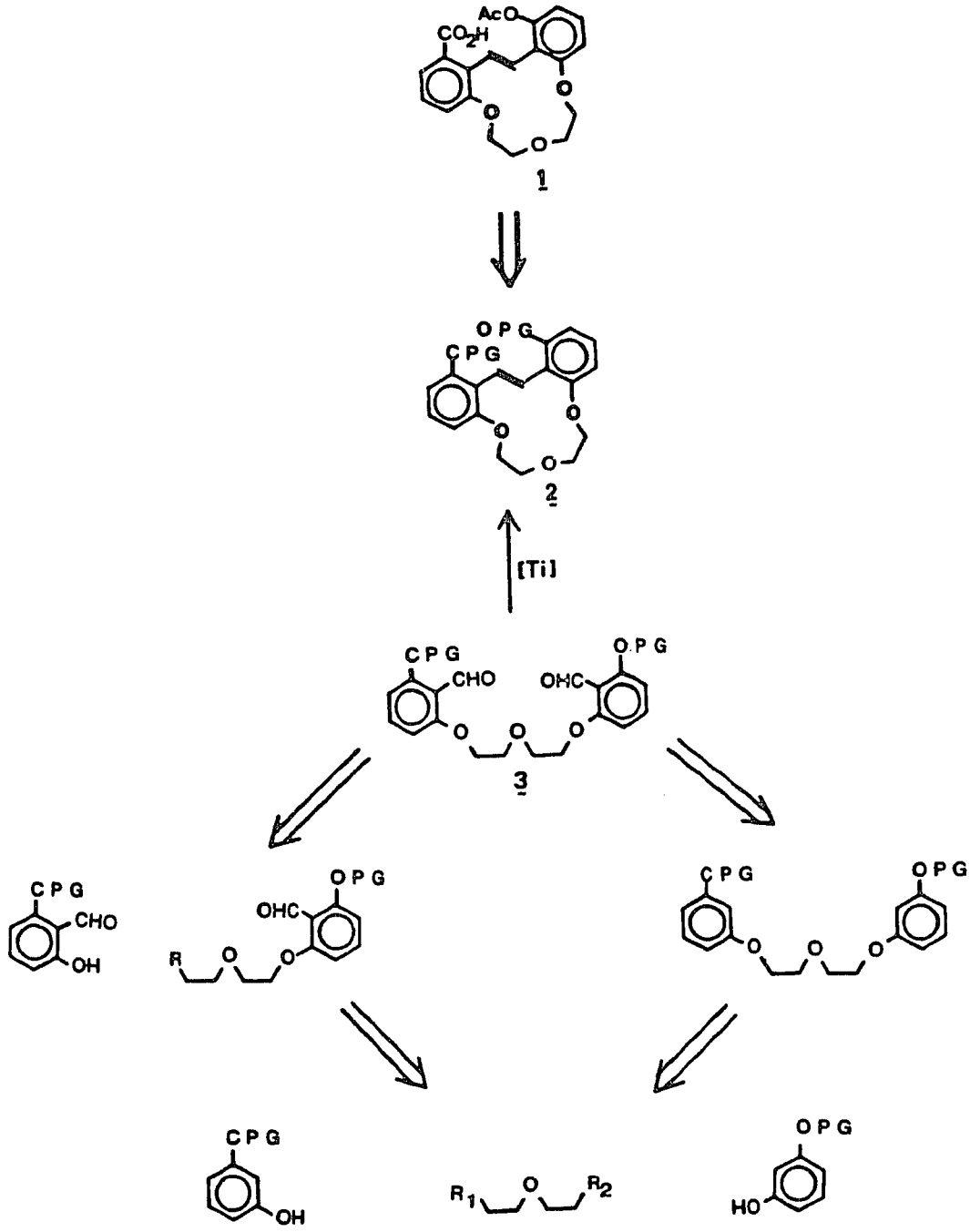

Figure 13. Antithetic scheme for the preparation of 1. CPG and OPG refer to protecting groups for the carboxylic and phenolic groups, respectively.

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take advantage of the cyclometallations.[72] This name has been proposed because the mechanism generally accepted for this group of reactions calls for the formation of a cyclic bond arrangement involving the metal, the carbon atom to which it will eventually be bonded, and a suitably placed atom or functional group linked to the carbon atom and associated, generally via coordination to the attacking metal. The cyclic nature of the reaction is commonly invoked to explain both the high yields and the high regioselectivities observed. Once a C-metal bond has been formed, the metal is displaced by a suitable electrophile. Alkyl halides or unsaturated functional groups have been utilized for this purpose.

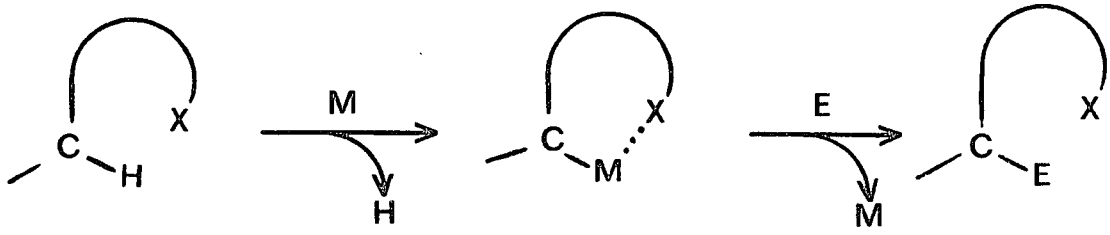

Figure 14. General scheme for a cyclometallation followed by the displacement of the metal by an electrophile.

Among cyclometallations, ortho-lithiations, in particular, have been very successfully employed towards this goal.[73] In these reactions, a lithium hydrogen exchange is biased towards a specific carbon-hydrogen bonds *via* strategically placed electron-donor atoms. The lithium atom can be later displaced by reaction with *N,N*-dimethylformamide (DMF) to form aldehydes in high yields. A shortcoming of

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this reaction is that the same high basicity and nucleophilicity of the organolithium reagents and intermediates that make it so useful forces one to protect any alternative acidic or electrophilic site in the substrates.

Both synthetic routes seem feasible. However, there are several advantages on the dilithiation route. First, the independent synthesis of both aldehydic units requires the extensive use of elaborate protection-deprotection schemes since it is necessary to selectively liberate one of the functional groups while keeping the other protected. This could prove to be very complicated, since most of the easily added and removed protecting groups are acid sensitive.[74] Second, the protection of the phenolic groups would likely be made with acetals to take advantage of their ortho-directing abilities in metallation reactions.[73] This clearly suggests that the ether linkage between the two aldehydes could serve the same purpose and avoid several deprotection steps, allowing for an overall more efficient synthesis of the required compound.

On the other hand, there are definite advantages of conducting both syntheses simultaneously. No precedent could be found in the literature for double lithium-hydrogen exchanges such as the one proposed in the dilithiation synthetic route, and in the case of this reaction not being possible, the separate monolithiation of each aromatic ring should offer a more time-proven, albeit more tedious alter-

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native. Also, most of the intermediates required are common to both routes. Furthermore, the reactions in both cases are variations on the same basic conversions, and very likely the same experimental conditions could be applied to most of them. Finally, several alternative synthetic pathways to the desired models, either stilbenes or any other two-carbon bridged *bis*(aromatic) species, can be envisioned through the intermediates generated in the course of these syntheses. This is further expanded in the Appendix to this dissertation.

Before launching into the synthesis of 1, a literature search revealed that most of the aromatic-aliphatic mixed ether syntheses available were both relatively low yielding and had very cumbersome work-ups.[75] Also, there were only a few examples of stilbenes whose crystal structures[76] or conformations in solution were investigated.

On these grounds, the syntheses of a series of simple stilbenes analogous to 1 would be highly advantageous. These experiments would allow us to test the feasibilty of utilizing the titanium reaction to close the desired rings utilizing simpler (and easier to prepare) intermediates, before investing too much time and effort in the preparation of the highly substituted intermediates to 1.

In addition to this, it would be possible on these simpler models to find adequate ways to prepare the aryl-alkyl ethers in high yields. An additional bonus of the prepara-

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tion of unsubstituted cyclic stilbenes is to learn more about their structure and conformation.

I.4 Research Plan. The goal of this research is the design and synthesis of an intramolecular model of enzymatic catalysis incorporating a carboxylate as a general base in a fixed geometric arrangement which would allow it to take full advantage of its basicity by constricting it to accept a proton in the syn orientation. Simultaneously, further theoretical studies on the syn-anti conformational isomerism of carboxylic acids are undertaken with the hope of increasing our understanding of the relative energetics, particularly on the effects of solvation in this equilibrium.

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CHAPTER II. *Ab Initio* Calculations on the Effects of Solvation in Formic Acid Conformations.

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II.1. INTRODUCTION. The orientation of molecules in a diffusion complex is generally believed to be an important factor for the success of a reaction. Quantifying the contribution from orientation has been a subject of considerable debate.[44] In particular, the orientation of a group may dictate its efficacy as a catalyst. Is there a stereoelectronic effect in protolytic catalysis by carboxylate? It has been shown in the preceeding chapter that this is possible.

The question concerning carboxylate is summarized in the cycle shown in Figure 7. The two conformational minima for carboxyl, syn and anti form upon ionization the same ion, carboxylate. The reverse reaction, protonation of carboxylate, can occur from any direction, but only one direction leads to the minimum energy conformation of the carboxyl. Furthermore, the energy difference among the two orientations in water should be reflected in the rates of the reactions on which carboxylate acts as a protolytic catalyst.[49]

Experimental data[77] in the gas phase and theoretical calculations[78] for the simplest carboxylic acid, formic acid, reveal that the syn orientation is more stable than the anti. These results are summarized in Tables 1 and 2. The numerical value of the energy difference between the conformers is, however, not agreed upon. A ΔE of 4 to 5 kcal/mol seems to be a reasonable estimate based on the measurements by Hocking[50] and the calculations of Csizmadia,[51] Allinger,[78k] and Zirz.[78o]

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Table 1. Experimental studies on the conformations of formic acid. Energies are given in kcal/mol.

YEAR	ΔE	ΔE‡	METHOD OF DETERMINATION	REF.
1957		17.0	Microwave Spectroscopy.	77a
1959	2.00	10.9	IR Spectroscopy.[a]	77b
1964	>4.0		Microwave Spectroscopy.[b]	77c
1973			IR Spectroscopy.[c]	77d
1976	4.09	13.8	Microwave Spectroscopy.[d]	77e

(a) Population vs. temperature study. (b) Anti conformer was not detected in this study. (c) Anti observed as a transient species in the reaction of ozone with dichloroethene. (d) Definitive structural assignment.

In what is considered the definitive elucidation on the structure of both conformers in the gas phase, Hocking and Bjarnov[50] calculated the dipole moments for the structures they obtained. The calculated dipole moments were 4.46 D for the anti and 1.78 D for the syn conformation. This suggests an additional complication. In water, or any other polar solvent, it would be expected that the most polar conformation would be stabilized better by its more favorable interaction with the solvent. In this case, this could mean that the additional interactions on the more polar anti conformation of formic acid on solvation could compensate for its intrinsic relative instability.

Among all other experimental studies, the results of Hisatune and Heicklen[77d] are of particular relevance to this issue. In their experiments they were trying to detect both syn and anti isomers of formic acid by hydrolyzing, in gas phase, the products of ozonolysis of *cis* and *trans* dichlo-

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roethene. When this reaction was conducted in the stoichiometric amounts of water vapor, both isomers were detected. But when excessive moisture was allowed in the system, only the syn isomer was detected. This seems to indicate that the direct interconversion between syn and anti by rotation around the C-O single bond is not a kinetically fast process, while introduction of additional water molecules facilitates the interconversion considerably, since only the more stable conformer was observed. Given that it is highly improbable that solvation lowers the barrier for a rotation, this experiment suggests a change in the interconversion mechanism on addition of more than stoichiometric amounts of water.

The effects of solvation on the conformational isomerism of carboxylic acids have not been addressed by theoretical methods. Of all the previous theoretical studies on conformational analysis found in the literature, only that by Schafer et al[78p] touches upon the effects of solvation formic acid. In their calculations, these authors introduced one molecule of water which they linked by hydrogen bonds to both the oxygens in formic acid. This additional interaction caused an energy difference of *ca* 16 kcal/mol between the isomers. Although this is not likely to be the correct number for a fully solvated species, it does give an indication that the energy difference will not be completely offset by solvation.

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These measurements and calculations, however, are relevant only when compared to gas phase observables. Since most

Table 2. Previous theoretical studies on the conformations of formic acid. Energies are given in kcal/mol.

YEAR	ΔE	ΔE‡	METHOD OF CALCULATION	REF.
1968	<0	2.30	EHT	78a
1971	1.88	3.54	EHT	78b
1971	2.00	4.66	CNDO	78b
1972	1.27	5.32	CNDO	78c
1968	>0	34.9	CNDO/2	78a
1968	0.56		CNDO/2	78d
1975	1.99	4.65	CNDO/2	78e
1975	2.23	6.78	CNDO/2-NO[a]	78e
1971	2.27	6.06	INDO	78b
1972	1.76	7.35	INDO	78c
1972	1.97		INDO	78f
1974	1.97	6.45	INDO	78g
1975	2.27	6.06	INDO	78e
1975	2.64	9.72	INDO-NO[a]	78e
1972	2.65	13.4	NDDO	78c
1968	8.10		Ab Initio GTF	78h
1970	8.10	13.00	Ab Initio GTF(5)	78i
1970	9.46	14.20	Ab Initio GTF(52/2)	78j
1977	4.73		Ab Initio STO-3G	78k
1979	4.46	9.61	Ab Initio STO-3G	51
1972	6.30	12.11	Ab Initio 4-31G	78l
1981	6.65		Ab Initio 4-31G	78m
1972	13.20	18.70	Ab Initio FSGO[b]	78n
1981	5.00	14.70	Ab Initio(SCF,DZP+CEPA)	78o
1982	15.85		Ab Initio 4-21G*[c]	78p

(a) A Valence-Bond Algorithm was introduced into the SCF subroutine of these programs. (b) Fragments gaussian orbitals. (c) Monohydrated formic acid.

organic and all enzymatic reactions occur in solution, aqueous solution in the latter case, an estimate of the relative stabilities of the confomations of carboxylic acids in aqueous media is highly desirable. Given that an experimental measurement of the energy difference between the two con-

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formers is not available in water, a theoretical approach has been employed to elucidate the problem. Although a quantitative answer is unlikely, the trend in relative energies in going from gas phase to solution should be revealed.

II.2. COMPUTATIONAL DETAILS. All calculations were done using the GAUSSIAN 80 series of programs.[79] Structures were optimized with *ab initio* RHF calculations using different basis sets and gradient optimizations. The only geometrical constraint on these optimizations was keeping the hydrogen bonds linear (O-H-O angle=180°). This was done to keep the number of variables within the limit of 50 imposed by the program.

The geometries were initially optimized using the STO-3G basis set,[80] then the split valence 3-21G[81] and 4-31G[82] basis sets consecutively, unless a different sequence is explicitly specified. Single point calculations were then conducted on the 4-31G optimized geometries utilizing the 6-31G** basis set (6-31G**//4-31G)[83] which is a split valence basis set supplemented with d orbitals in carbon and oxygen atoms, and p orbitals in hydrogen atoms.[84,85]

II.3. RESULTS AND DISCUSSION.

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II.3.1. Obtention of the Optimized Structures. The first step in the construction of complete solvated formic acid structures was the obtention of adequate geometries for the isolated conformers. These geometries were obtained by minimizing the total energy at the different levels of theory. Not very surprisingly, the energy difference obtained at the STO-3G level (4.44 kcal/mol) was very similar to those reported previously (4.73[78] and 4.46[51] kcal/mol) using the same basis set. This difference, though, increased to 5.69 kcal/mol when the energies for the isolated conformers were evaluated using the 6-31G** basis set on the 4-31G optimized geometries. These split-valence basis sets are known to be more reliable for calculations of both energies and stuctures[86] in cases were O-H bonds are involved.

After a satisfactory geometry for the isolated formic acid conformers was obtained by optimization at the 4-31G level, the cybotactic region+ was built around it using hydrogen bonds to the carboxyl proton and the lone pairs on the oxygen atoms to locate initially the water molecules. Based on previous calculations[88] on which single water molecules were anchored on the different possible locations around the formic acid molecules, a single water molecule was initially placed in an orientation that would allow it to act as a hydrogen bond acceptor for the carboxyl proton.

+: This name has been suggested for the first solvation shell[87] and is adopted here because of its more adequate etymological meaning.

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These moieties were then optimized at the various levels of theory to arrive at a final energy difference of 4.95 kcal/mol at the 6-31G**//4-31G level. This value is considerably smaller than the one obtained by Schafer et al[78p] using the 4-21G* basis set.

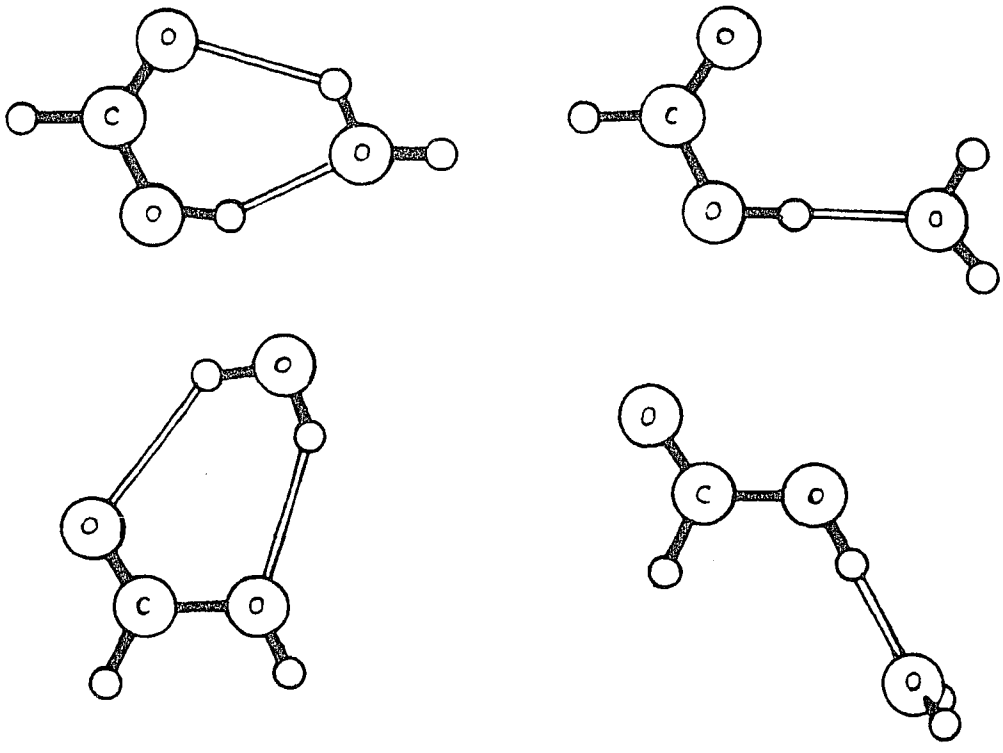

Figure 15. Comparison of formic acid monohydrates between this work (at right) and Schafer et al.[78p] (at left). Solid lines represent covalent bonds, hollow lines indicate hydrogen bonds.

This discrepancy, rather than being caused by a basis set effect, is probably due to the different fashion in which the water molecules are disposed on the formic acid

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(see Fig 15). In the calculations by Schafer et al., the water molecules are attached in a different manner to the syn and anti conformers. In the anti molecule the water molecule is acting as a hydrogen bond donor towards both oxygen atoms, while in the syn conformation it is accepting a hydrogen bond from the carboxyl proton and donating towards the carbonyl carbon. The latter arrangement would allow it to disperse better the electron density. In our structures, on the other hand, the water molecules are attached to the different formic acids in equivalent fashion.

Next, two more water molecules were added to the previously obtained monohydrate in a donor fashion towards the carbonyl oxygen. When the structures were optimized at the STO-3G level, there was a great deal of movement on the water molecules attached to the carbonyl oxygen in the syn conformer. The final geometry of the trihydrate at this level clearly suggested the existence of a hydrogen bond relay cycle from the hydroxyl to the carbonyl oxygens through two water molecules. In the anti conformation, this is impossible. The existence of this hydrogen bonding network causes a much lower energy for the syn conformation through a more favorable charge dispersion.

Since the choice of the hydration in the carbonyl oxygen was arbitrary to a certain extent, it was felt that the energy difference obtained at this degree of hydration would not be a fair representation of the difference for fully

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solvated species, given that the geometries obtained were obviously biased for the syn conformation. Therefore, two more waters were attached, as hydrogen bond donors, to the hydroxylic oxygens in the formic acids.

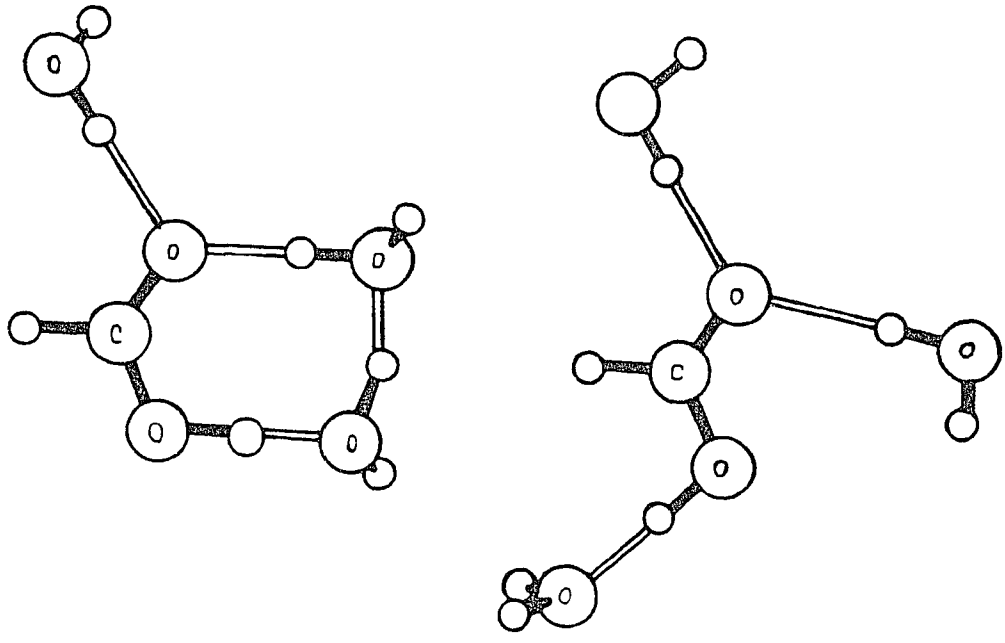

Figure 16. 4-31G Structures of the formic acids trihydrate conformers.

These pentahydrates were then optimized at the STO-3G level, which gave an energy difference of 11.94 kcal/mol. This value was suspect since close analysis of the geometry obtained for the anti isomer did not show any hydrogen bonding or interactions among the newly added water molecules, which were spatially close enough for this. These structures were then optimized at the 4-31G level obtaining the geometries depicted in Figure 17. These had clearly defined interactions between all the spatially close water mol-

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ecules. The final energies were obtained by a single point calculation using the 6-31G** basis sets on the 4-31G optimized geometries.

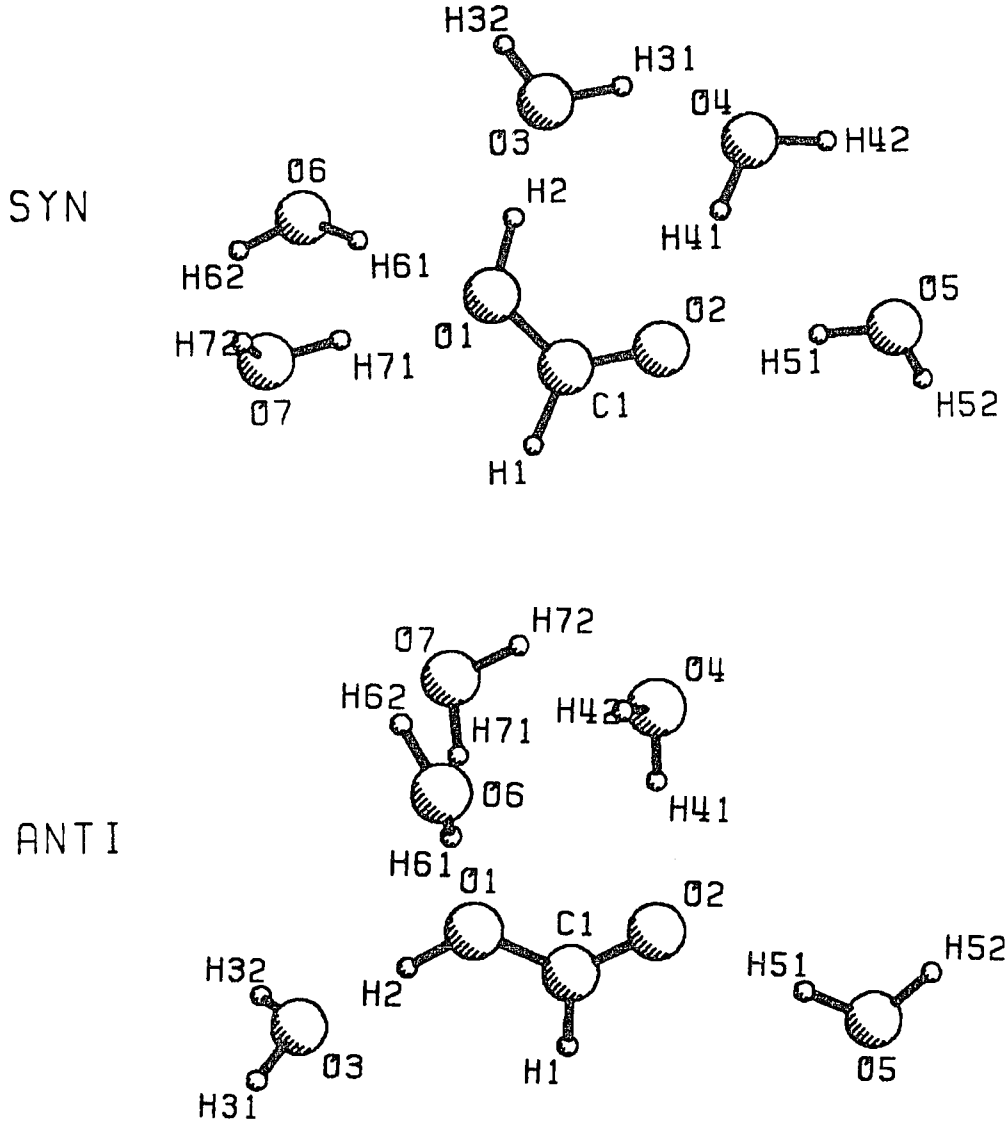

Figure 17. PLUTO Drawings of syn and anti formic acid pentahydrates. Structures were optimized at the 4-31G level.

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The final energies obtained at the different degrees of solvation according to the STO-3G, 4-31G, and 6-31G** basis sets are summarized in Table 3. The results at the 3-21G level were not included since they were intermediate between the ones obtained with the STO-3G and 4-31G basis sets, and neither pentahydrate was optimized at this level.

Table 3. Table of energies obtained for the different conformations and degrees of solvation of formic acid. Energies are given in kcal/mol (Hartrees).

MOIETY	STO-3G//STO-3G	4-31G//4-31G	6-31G**//4-31G
a-HCO_2H	-116,851.005 (-186.21080)	-118,265.331 (-188.46463)	-118,450.106 (-188.75909)
s-HCO_2H	-116,855.440 (-186.21787)	-118,272.221 (-188.47561)	-118,455.791 (-188.76815)
a-HCO_2H: H_2O	-163,903.656 (-261.19271)	-165,913.328 (-264.39528)	-166,164.670 (-264.79582)
s-HCO_2H: H_2O	-163,907.777 (-261.19928)	-165,919.730 (-264.40548)	-166,169.621 (-264.80371)
a-HCO_2H: $5H_2O$	-352,096.197) (-561.09158)	-356,484.122 (-568.08406)	-357,011.383 (-568.92429)
s-HCO_2H: $5H_2O$	-352,108.139 (-561.11060)	-356,493.865 (-568.09959)	-357,013.893 (-568.92829)

II.3.2. Effects of Solvation on the Energies. The energy differences for the syn and anti conformations of formic acid at the different levels of theory are given in Table 4. The 3-21G level results were not included for the same reasons given above.

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From Table 4 it is apparent that the energy difference between the conformers of formic acid did decrease upon solvation at the 6-31G**//4-31G level. This is a monotonic trend for this particular basis set. That is, the energy difference for the monohydrates is lower than that of the non-solvated species, and the difference for the pentahydrates is still lower. The latter result is particularly surprising when compared with the trends observed at the other levels of theory.

Table 4. Relative energies (Eanti-Esyn) in kcal/mol for the different degrees of solvation of formic acid.

MOIETY	STO-3G//STO-3G	4-31G//4-31G	6-31G**//4-31G
HCO_2H	4.435	6.890	5.685
$HCO_2H:H_2O$	4.121	6.082	4.951
$HCO_2H:5H_2O$	11.942	9.743	2.510

The decrease in energy difference between conformers is observed at the STO-3G//STO-3G and 4-31G//4-31G levels on going from the free to the monohydrated species. However, the energy difference increases for the pentahydrates when using these basis sets. This evolution of the energy differences would be expected based on the dipole moments of the syn and anti conformations of formic acid. When a single molecule of water is attached to the acidic proton on each conformer, the more polar anti form is expected to be better

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stabilized by this interaction, thereby reducing the energy difference between the conformers. Once the full solvation shell has been added one would expect this localized interaction to play a less important role.

It should as well be kept in mind that at the 6-31G**//4-31G level no structure optimization at the higher level is made. That is, the structure optimized at the 4-31G level is utilized in a single point calculation of the energy utilizing the 6-31G** basis set. Although this approach seems to be acceptable in the free formic acid and the monohydrated species in which a small reduction of the energy differences is obtained (1.2 and 1.1 kcal/mol, respectively), the very large decrease (7.2 kcal/mol) on the pentahydrates does not seem to be consistent with the other cases. The obvious solution, optimization of the pentahydrates structures at the 6-31G** level, is unfortunately prohibitive in terms of cost and computational times required.

The absolute magnitude of the energy difference obtained from the single point calculations at the 6-31G** level in the pentahydrates is not consistent with the results at lower levels of hydration. It is, however, a good indication that even in solution phase the syn conformer of formic acid is more stable than the anti. Although there was some reason to believe that the additional stabilization of the more polar species (the anti conformer) could completely override the intrinsic stabilities, the observed energy dif-

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ferences at the various levels of theory indicate otherwise. According to these calculations, then, the syn orientation of formic acid is more stable than the anti in aqueous solution.

II.3.3. Effects of Solvation on the Structures. The analysis of the final optimized structures for the various degrees of solvation gives some very interesting insights

Table 5. Geometrical parameters of the formic acid conformers at different degrees of solvation. Geometries were optimized at the 4-31G Level. Bond lengths are in are in Angstroms, angles in degrees.

	HCOOH		$HCOOH:H_2O$		$HCOOH:5H_2O$	
	syn	anti	syn	anti	syn	anti
LENGTHS						
H1C1	1.0723	1.0799	1.0740	1.0821	1.0729	1.0769
C1O2	1.2003	1.1931	1.2085	1.1966	1.2159	1.2065
C1O1	1 3419	1.3462	1.3255	1.3299	1.3169	1.3265
O1H2	0.9560	0.9507	0.9759	0.9664	1.0126	0.9809
ANGLES						
O1C1O2	124.608	122.471	124.850	123.707	124.941	121.969
H1C1O1	110.433	114.596	111.626	114.407	112.614	115.644
C1O1H2	114.897	116.672	114.519	116.810	119.682	118.509
TORSIONS						
H2O1C1H1	180.000	-0.332	179.978	0.000	182.552	-1.404
H2O1C1O2	0.000	179.682	-0.027	180.000	3.054	178.566

into the effects that hydrogen bonding solvents have on polar substrates. The final stuctural parameters for the formic acid substructures are summarized in Table 5, and can be better understood when analyzed together with the final charge distributions obtained from the Mulliken population

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analyses.[89] The residual charge distributions are given in Table 6.

From Table 6 it can be seen that as more water molecules are added, the electron density is delocalized more extensively among all the atoms of the central formic acid moiety. Two notable exceptions are C1 and H1 whose charge density actually decrease at the monohydrated stage. Both of

Table 6. Residual charges (in electrons) for the formic acid conformers at different degrees of solvation at the 6-31G**//4-31G level.

	HCOOH		$HCOOH:H_2O$		$HCOOH:5H_2O$	
Atom	syn	anti	syn	anti	syn	anti
(C-)H1	+0.145	+0.109	+0.124	+0.091	+0.161	+0.148
C1	+0.605	+0.607	+0.604	+0.603	+0.653	+0.642
(C=)O2	-0 526	-0.496	-0.568	-0.529	-0.611	-0.563
(C-)O1	-0.592	-0.582	-0.635	-0.628	-0.692	-0.667
(O-)H2	+0.369	+0.362	+0.441	+0.427	+0.499	+0.468

these anomalies are understandable, since the latter two atoms are the ones less affected by the addition of a single water molecule. On addition of the remainder of the solvent shell, the waters disperse the electronic density better. The charge separation phenomenum is paralleled by changes in bond lengths. That is, as the charges disperse better on hydration, bond lengths increase.

The only bond length that does not follow this trend is C1O1. However, as the electron density decreases in H2, the O1H2 bond is weakened rapidly. This forces the molecule to

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absorb the excessive density in the C101 bond, making it actually shorter. From Tables 5 and 6 it can be seen that on pentahydration the charges in H2 have increases of +0.130 for the syn conformer and +0.106 for the anti, simultaneously, the O1H2 bond has stretched out by ca. 0.06 (syn) and 0.03 Å (anti). These weakenings cause the C101 bond to shorten by 0.025 (syn) and 0.020 Å (anti).

In general, the larger changes both in charges and structure occur in the syn conformation of formic acid. This is very likely due to the more localized interactions of the water molecules with this particular conformation.

II.3.4. Structure of the Solvent Shell. The cybotactic region of formic acid is the determining factor for the decrease in the energy difference. Its fine structure does reveal some interesting details. The most important structural moieties, the central formic acids and the water molecules bridging the hydroxylic and carbonyl oxygens are illustrated in Figure 18.

Of both conformations of formic acid, syn shows the stronger hydrogen bonds. The hydrogen bond relay system shown above has shorter internuclear separations and wider angles than in the anti conformer. These distances agree quite well with experimental studies in the solid phase (1.75-1.95 Å[90]) and both theoretical studies on water dimers (O-O 3.0 Å) and experimental studies on Ice I (O-O 2.75 Å).[91] The only angle which was allowed to vary in this work

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was rather small (145.2°) as compared with a 168° mean for experimental measurements in solid phase,[90] but since it is an internal angle in a cycle which has two fixed angles of 180°. Unfortunately, these constraints are forced by limitations on the program and computational times.

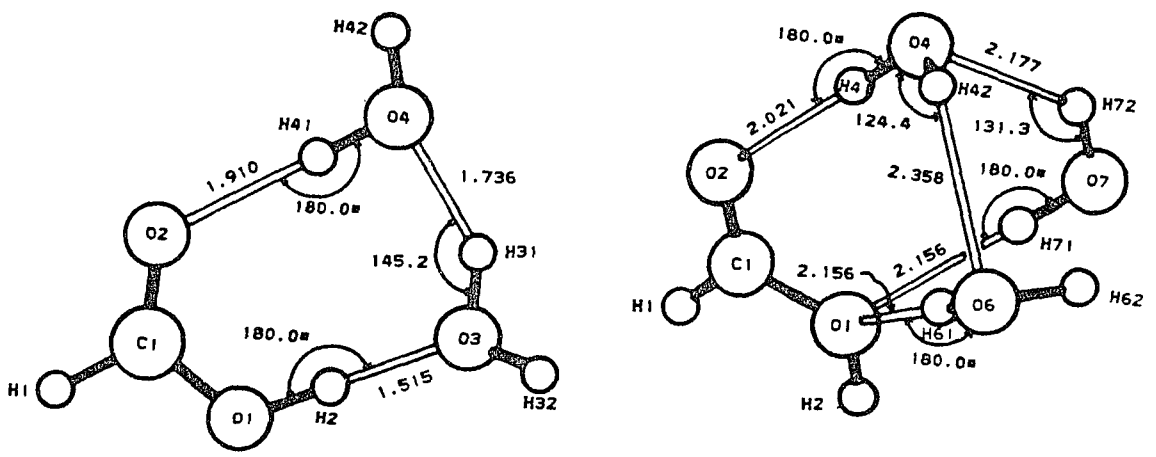

Figure 18. Structural details of the hydrogen-bonded cycles.

The anti conformation, on the other hand, has much longer internuclear separations and smaller angles. Some of these distances are well above the normal values for hydrogen bonds. However, they are close enough for a stabilizing interaction. The Mulliken population analysis shows a sig-

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nificant electron population between the oxygen and hydrogen atoms involved. The larger number of hydrogen bonds offsets the advantage of the stronger interactions present in the syn conformation.

The analysis of the residual charges shows a definite correlation between the total residual charges in each water molecule and its role in the hydrogen bond(s) in which it is involved. In the syn-pentahydrate, the central formic acid has a total residual charge of +0.010 e, while the water molecules H3103H32 and H4104H42 have charges of +0.030 and +0.003 e, respectively. This two water molecules are the only ones in this conformation that act as hydrogen bond acceptors, the latter one being also a donor. The remaining water molecules, H5105H52, H6106H62, and H7107H72 have charges of -0.011, -0.020, and -0.013 e, respectively.

In the anti conformation the central formic acid has a residual charge of +0.028 e and the sole water that acts only as a hydrogen bond acceptor (H3103H32) has a residual charge of +0.047 e, while H5105H52, which only behaves as a donor shows a -0.022 e charge. The remaining water molecules, H4104H42, H6106H62, and H7107H72, have charge densities of -0.016, -0.007, and -0.028 e, respectively. It should be noted that the highest residual charge observed is located in a double-donating water (-0.028 e, H7107H72), and the lowest are in waters which act both as donors and acceptors.

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II.4. CONCLUSIONS. The most important result of these theoretical studies is, obviously, the obtention of a definitely positive energy difference between the syn and anti conformers of the pentahydrated formic acid, being the syn the more stable form. The absolute magnitude obtained at the 6-31G**//4-31G level, 2.51 kcal/mol, does not follow the trends observed at the lower degrees of solvation. The results from these calculations show that, although there is an additional stabilization for the more polar form on going from isolated molecules (i.e. gas phase) to a water solvate, it is not enough to completely offset the intrinsic energy difference. Furthermore, this additional interaction is caused by the incorporation of another water molecule into a fairly strained cyclic system. It should be kept in mind that the energy differences obtained by this calculations are not a free energy difference (ΔG) that could be directly utilized in the thermodynamic equations in Chapter I. The energy calculated does not reflect any vibrational contributions, and therefore, it does not give any indication on the effect of the entropies involved.

Being that, according to these calculations the syn conformer of pentahydrated formic acid is still more stable than the anti, the corresponding formate anion should be a stronger base when accepting a proton in the syn orientation. That is to say, *ab initio* calculations support the existence of a stereoelectronic effect in reactions that

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show general base catalysis by carboxylate in aqueous solution.

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CHAPTER III. Syntheses of Stilbene Cycles.

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III.1. INTRODUCTION. In the preceding chapters the possibility of the existence of stereoelectronic effects on carboxylate general base catalysis was discussed and supported by theoretical calculations. The model compound 1 necessary for the experimental testing of this effect proposed in Chapter I requires extensive synthetic efforts. The initial part of these efforts, namely the syntheses of simpler, non-functionalized compounds analogous to the desired model 1 is detailed in this chapter.

The previously outlined synthesis of 1 relies heavily on the possibility of using the low-valent titanium carbonyl coupling reaction to close a stilbenic ring. No precedent of this reaction was found in the literature. Furthermore, the yields in the titanium reaction, as originally reported by McMurry[68], have shown some unexplained variations[92] which are apparently dependent on the particular batches of the reagents utilized. Several modifications of this reaction, in which a different reducing agent is utilized, have been proposed.[92-97] McMurry recommends the use of zinc-copper couple,[93] lithium metal[94] or potassium metal[92] to generate the low-valent titanium from $TiCl_3$. The use of magnesium,[95] zinc dust[96] or magnesium-mercury amalgam[97] have also been reported by other workers.

In addition to these problems, most of the preparations of aromatic-aliphatic ethers found in the literature suffer of several disadvantages, namely low yields (30 to 50 %),[98]

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cumbersome isolation procedures (chromatography is routinely required),[99] or the need to utilize excessively strong bases (i.e. potassium *tert*-butoxide[100]) for the deprotonation of the phenolic moiety. Some of the highest yielding (60-70 %) preparations require the formation and isolation of the sodium[101] or potassium[102] phenoxide, which are then reacted with the electrophile in boiling *N,N*-dimethylformamide (DMF). Since the yields on the formations of the salts are on the order of 90 %, the yields from the free phenol in these procedures are really in the 50-60 % range. Therefore, in order to determine the applicability of either of these reactions or find adequate alternatives to them, a program of research to synthesize unsubstituted simpler analogues of 1 was launched.

III.2. RESULTS AND DISCUSSION.

III.2.1. Syntheses of Cyclic Stilbenes. The primary phase of this program consisted in the development of a more convenient synthesis of ethers which would not suffer from the disadvantages mentioned above, and would allow us to synthesize mixed ethers in high yields. The most attractive preparation of these ethers found in the literature was the method reported by Vogtle and coworkers[104] which called for the use of potassium hydroxide as the base in 1-butanol solvent. When these reaction conditions were tried with salicy-

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laldehyde and *bis*-(2-chloroethyl)ether, the *bis*(benzaldehyde) ether product, **4h**, could be isolated (30 %) as a dark red oil. Changing the leaving group to a bromide increased the yield to a 52 %. However, the butanol used as solvent had to be separated from the product by distillation. It seemed that the high temperatures at which this separation was done would be detrimental to the product.

Since separation of the butanol could not be effected by aqueous extractions, different solvents and bases were tried under similar conditions. Refluxing KOH in DMF did not yield any product after 27 h, and only unchanged starting material was recovered from reactions with triethyl amine in methylene chloride or KOH in aqueous THF. KOH was not soluble in dioxane even under vigorous reflux for 10 h, but addition of HMPA did bring it into solution. Addition of salicylaldehyde and *bis*-(2-bromoethyl)ether gave a deeply red solution with a finely divided white precipitate. After 4.75 h the reaction mixture was cooled down, diluted with water and extracted with CH_2Cl_2. The organic extracts yielded large amounts of product along with the HMPA cosolvent which, in our hands, could not be completely removed from the product. Still, by NMR analysis, the yield could be estimated at ca 65 %. Furthermore, it was observed that a very favorable partition between aqueous KOH and ether could be utilized to separate the HMPA from the product.

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Following these results, the etherification was conducted in dioxane-HMPA solvent. When the crude reaction mixture was extracted with ether instead of methylene chloride, and additional washings with 5 % aqueous KOH were used to isolate the product, HMPA-free pure product crystallized spontaneously on removal of the solvent of the organic extracts. After these washings were incorporated into the routine isolation procedure, a higher yield was obtained on the use of NaOH over KOH as the base in the reaction itself (73 %). Changing the leaving groups to tosylates increased the isolated yield to 89 %.

Table 7. Summary of Experimental Conditions and Yields in the Preparation of Bis(carbonyl) Ethers.

Phenol	Electrophile	Product	Yield (%)
Salicylaldehyde	$(TsOCH_2CH_2)_2O$	**4h**	89
	$(BrCH_2CH_2)_2CH_2$	**5h**	97
	$(BrCH_2)_2(1,2\text{-}C_6H_4)$	**6h**	76
2-Hydroxyacetophenone	$(MsOCH_2CH_2)_2O$	**4m**	89

These reaction conditions were also applied to the reaction of salicylaldehyde with other alkylating agents like 1,5-dibromopentane and 1,2-*bis*(bromomethyl)benzene to yield the *bis*(benzaldehyde)ethers **5h** and **6h** in 97 % and 76 % yields, respectively. When the phenol was changed to 2-hydroxyacetophenone, reaction with diethylene glycol dimesylate gave the expected product, **4m** (89 %). These results are summarized in Table 7.

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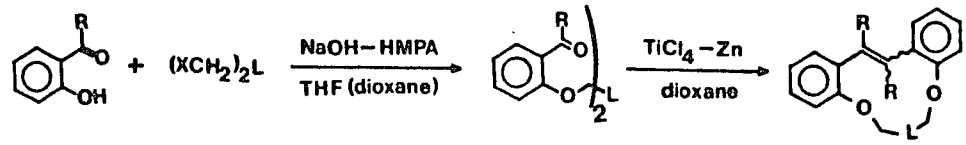
Once these compounds were in hand and a convenient and high yielding procedure for their synthesis was available, the viability of the different variants of the titanium-induced ring closure to form the corresponding stilbene cycles had to be tested in these ethers. The modification by Mukaiyama and coworkers,[96] in which zinc dust was utilized as the reducing agent, was initially chosen over McMurry's original reaction ($TiCl_4/LiAlH_4$) due to the unexplained variability mentioned above. When a solution of **4h** in dioxane was added dropwise to a suspension of the low-valent titanium, prepared according to Mukaiyama's procedure, a high yield (83 %) of the desired product, **7h**, was obtained as a mixture of



R = H	L = $-CH_2OCH_2-$	**4h**	**7h**
H	$-(CH_2)_3-$	**5h**	**8h**
H	$1,2-C_6H_4-$	**6h**	
CH_3	$-CH_2OCH_2-$	**4m**	**7m**

Figure 19. Syntheses of stilbene cycles.

the *Z* and *E* stereoisomers. Interestingly, no products of intermolecular condensation could be detected even when the reaction was not conducted in high dilution nor special equipment for very slow additions was utilized.

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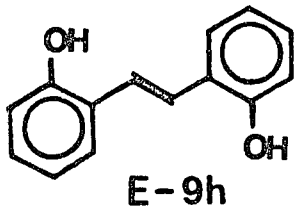
Table 8. Summary of experimental conditions and yields in the preparation of stilbene cycles.

Bis(carbonyl) ether	Reflux time, h	Product	*Z*/*E*	Yield (%)
4h	6.3	*Z*- and *E*-**7h**	40/60	83
5h	20.0	*Z*- and *E*-**8h**	62/38	64
6h	3.5	*E*-**9h**	0/100	74
4m	16.0	*Z*- and *E*-**7m**	59/41	82

When the same reaction was tested on **5h** and **4m** good yields of the cyclic stilbenes were obtained, but when **6h** was subjected to the same conditions only (*E*)-1,2-*bis*(2-hydroxyphenyl)ethene (*E*-**9h**) was isolated instead of



E-9h

the expected stilbene cycle. The yields, isomeric compositions (by NMR), and reflux times are summarized in Table 8. With the exception of the xylene-bridge on **6h**, this reaction sequence provided an easy and high yield two-step procedure to convert phenolic carbonyls into stilbene-containing cycles. The overall yields for **7h**, **7m**, **8h**, and **9h** were 74, 61, 73, and 56 % ,respectively. The *Z*-isomer was predominant in **8h** and **7m**, but this did not pose any problems since the mixtures were easily resolvable by either fractional recrystallization or standard chromatographic methods. It was encouraging to note that the highest yields

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were obtained on **7h** and **7m** possessing the diethylene glycol bridge, which was the initial choice for the final synthetic goal, compound **1**.

All the compounds prepared were identified by their ^{1}H and ^{13}C NMR, infrared, ultraviolet, and mass spectra. In addition, X-ray structures[105,106] were determined for at least one compound in each isomeric pair of the final stilbene cycles.

III.2.2 NMR Data. The NMR spectra, both ^{1}H and ^{13}C, for all compounds prepared show symmetric patterns, that is, only four aromatic protons and six aromatic carbons are observed. This result is in apparent contradiction with the X-ray diffraction data, which show clearly unsymmetric structures for *E*- and *Z*-**7h**, *E*-**8h**, and *Z*-**7m**. This has been suggested[105] to be due to a rapid conformational equilibration among rotamers *via* rotation around the single bonds connecting the aryl rings to the central double bond.

There are several consistent differences between the geometrical isomers for each structure in the NMR spectra. The vinylic proton resonance is further downfield for the *E*- isomer in each pair (δ 7.84 and 7.69 for **7h** and **8h**, respectively) than for the *Z* (δ 6.66 for both compounds), this is also observed in stilbene itself.[107] The vinylic carbon resonance is further downfield for the *Z*- isomers (δ 127.4, 130.6, and 128.3 for **7h**, **7m**, and **8h** , respectively) than in the *E*- series (δ 126.5, 130.5, and 126.5

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for **7h**, **7m**, and **8h**, respectively). The chemical shift difference in the olefinic protons is large enough that it can be used to identify the isomers. The chemical shift differences in ^{13}C NMR , on the other hand, are too small to be of practical use in the assignment of stereochemistry.

$$\underset{}{-O-CH_2-CH_2-CH_2-CH_2-CH_2-O-}$$
$$\quad\quad\quad\quad\quad\quad\quad\quad 9 \quad 10 \quad 11$$

There are some interesting effects on the ^1H NMR spectra spectra of the pentanediyl-bridged stilbene cycles, **8h**. In particular, the resonances due to the three central methylenes on the pentane bridge show some large chemical shift variations. The protons on carbons 9 and 11 are equivalent, but the geminal protons on each methylene can exhibit different chemical shifts because they are part of a ring.

On the precursor dialdehyde, **5h**, the chemical shifts for the central methylenes are δ 1.90 for 9 and 11, and δ 1.70 for 10. The lower chemical shift for 10 would be expected, since it is further separated from the only substituents, the oxygen atoms. On the closed stilbenes, the protons attached to 9 and 11 appear at δ 1.43 for *Z*-**8h** and δ 1.85 for the *E*- isomer. Both of these chemical shift displacements show a shielding relative to the open-compound. On the other hand, the resonances of the central methylene (10), appear at δ 1.65 for the *Z*- isomer and at 2.05 for the *E*. The strong deshielding on the central methylene is due to its being restricted to lie in the deshielding region of the aromatic rings and the double bond.

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III.2.3 X-Ray Structures. The crystal structures of compounds *E*-**7h**, *Z*-**7h**, *E*-**8h**, *E*-**9h**, and *Z*-**7m** were determined by X-ray diffraction,[105,106] and are shown in Figure 20.

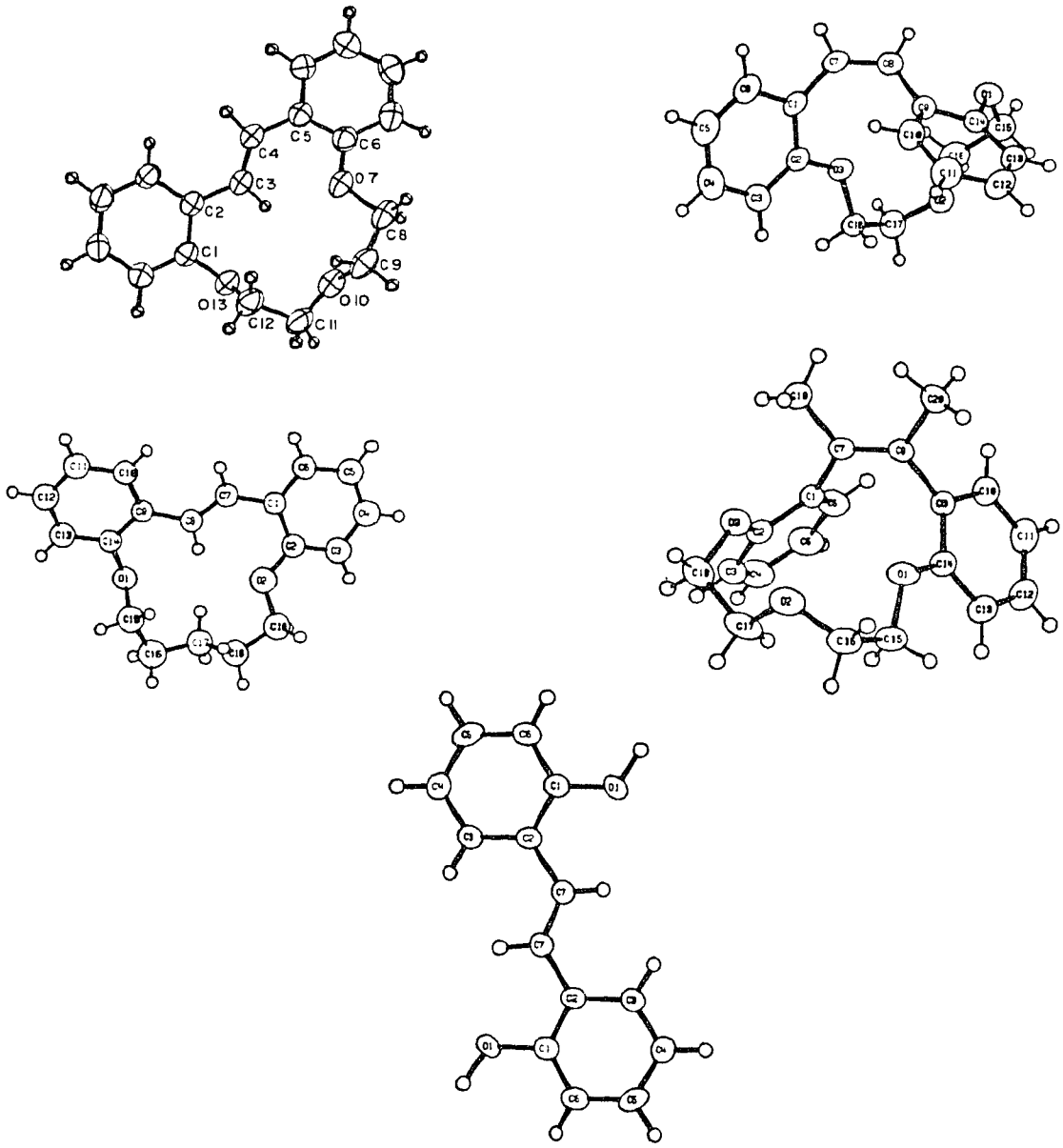

Figure 20. ORTEP drawings of the crystal structures of *E*-**7h** (top left), *Z*-**7h** (top right), *E*-**8h** (middle left), *Z*-**7m** (middle right), and *E*-**9h** (bottom).

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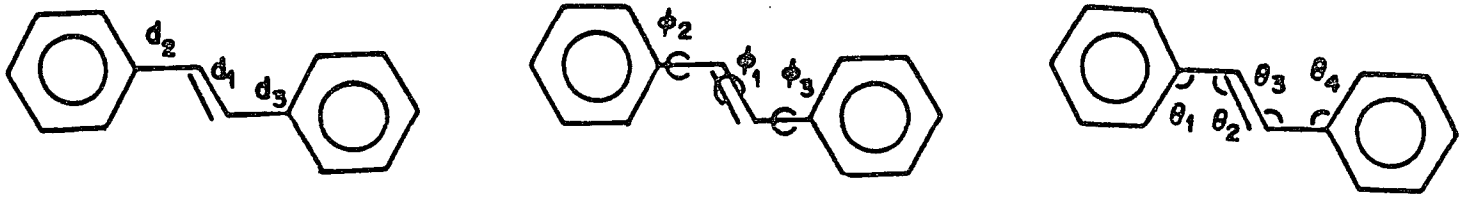
TABLE 9. Comparison of Geometrical Features of Stilbene Cycles and Other Stilbenes. Bond Lengths are Given in Angstroms, Angles in Degrees.

	E-STL[a]	*E*-7h[b]	*E*-8h[c]	*E*-9h[c]	*Z*-7h[c]	*Z*-7m	*Z*-DO[d]	*Z*-TC[e]
d_1	1.318(3)	1.326(2)	1.310(6)	1.328(4)	1.326(4)	1.332(3)	1.31(1)	1.33(1)
d_2	1.469(4)	1.461(2)	1.450(7)	1.476(4)	1.465(4)	1.508(3)	1.49(1)	1.464(9)
d_3	1.469(4)	1.471(2)	1.462(7)	1.476(4)	1.468(3)	1.494(3)	1.49(1)	1.46(1)
ϕ_1	180.0	−176.4	−176.2	180.0	−5.0	−5.7	−9.8	−5.0
ϕ_2	5.0	171.8	174.3	17.6	−52.0	−73.7	113.4	54.2
ϕ_3	−5.0	−17.0	−16.3	−17.6	145.3	125.0	118.2	54.5
θ_1	123.3(2)	119.4(1)	124.4(5)	122.1(3)	123.3(2)	121.1(2)	122.3(8)	121.7(7)
θ_2	126.7(2)	127.3(1)	129.5(5)	125.2(3)	128.6(2)	121.6(2)	121.9(7)	125.7(7)
θ_3	126.7(2)	128.2(1)	129.0(5)	125.2(3)	127.6(3)	123.3(2)	121.8(7)	124.6(7)
θ_4	123.3(2)	124.2(1)	120.4(3)	122.1(3)	120.5(2)	123.2(2)	121.7(8)	120.8(8)



(a): *E*-1,2-Diphenylethene, Ref. 108 (*E*-Stilbene). (b) Ref. 105.
(c): Ref. 106. (d): *Z*-2,3-Bis-(2-methoxyphenyl)-2-butene, Ref. 109.
(e): *Z*-1,2-Bis-(4-chlorophenyl)-1,2-dichloroethene, Ref. 110.

Complete crystallographic data and tables of atomic coordinates for these compounds are given in the Appendix 2. A comparison of the geometry of the double bond linking the aromatic rings with that of other stilbenes is presented in Table 9.

From the data in Table 9 it is apparent that there is a higher deviation of coplanarity between the aromatic rings and the central double bond in the compounds prepared here and stilbene itself. However, the acyclic bisphenol *E*-**9h** shows very similar dihedral angles around the double bond. This suggests that the distortions from planarity observed are due to the electronic effect of the oxygen atoms *ortho* to the vinylic moiety rather than to any steric constraints imposed by the cyclization.

III.3. CONCLUSIONS. A new experimental procedure for preparing ethers developed here permits the synthesis of aromatic-aliphatic ethers in high yields with very straightforward workups. When this procedure is combined with Mukaiyama's modification of the low-valent titanium induced coupling of carbonyls, a simple, high-yielding synthetic strategy for stilbene-containing cycles is obtained. If convenient synthetic routes to adequately protected functionalized aldehydes can be found, the synthesis of the desired model 1 should proceed easily through this route.

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III.4. Experimental Section.

General Procedures. Melting points were determined on a Electrothermal apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker WP-200 spectrometer operating at 200 and 50.3 MHz, respectively, and are recorded in $CDCl_3$ except where noted. All chemical shifts are expressed as ppm relative to internal TMS and coupling constants in Hz. IR spectra were obtained on a Perkin Elmer Model 621 grating infrared spectrometer and UV spectra on a Varian Associates Cary 118. Mass spectra were obtained by Mr. Don Patterson on a Hewlett-Packard Model 5985 GC-Mass Spectrometer and are recorded as *m/e*(relative intensity). Dioxane was dried by distillation from sodium. THF was distilled from sodium benzophenone ketyl. Salicylaldehyde, 2-hydroxyacetophenone, and diethylene glycol were purified by fractional distillation under nitrogen. Titanium tetrachloride was purified by refluxing over copper scouring pads, followed by distillation. Zinc dust was activated by succesively washing with 5% HCl, water, ethanol, ether, and drying it under vacuum. All the remaining reagents were used as received. All the glassware utilized was oven-dried at 140°C, assembled hot, and cooled under a rapid argon or nitrogen stream.

2,2'-[Oxybis(2,1-ethanediyloxy)]bisbenzaldehyde (4h) : A solution of 9.3 g (76 mmol) of salicylaldehyde in 75 mL of

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THF was added to a refluxing suspension of 3.2 g (80 mmol) of NaOH in 75 mL of HMPA (Aldrich). The mixture was refluxed for 1.3 h, then, a solution of 15.0 g (36 mmol) of diethylene glycol ditosylate[111] in 75 mL of THF was added dropwise over 15 min. The mixture was then refluxed for 3 h, cooled to 25°C, and filtered. The filtrate was diluted with 250 mL of H_2O and extracted with 3x100 mL of Et_2O. The combined organic extract was washed with 3x50 mL of 5% KOH and 100 mL of brine, dried over Na_2SO_4 and concentrated *in vacuo* to obtain 10.2 g (89.4 % yield) of a slightly yellowish powder: MP 66-67°C (Lit.[112] MP 75-76°C from MeOH-H_2O).

^{1}H NMR [$(CD_3)_2CO$] δ 10.51 (2H1, s), 7.84 (2H3, dd, J_1=7.7, J_2=1.9), 7.55 (2H5, ddd, J_1=8.4, J_2=7.4, J_3=2.1), 7.09-6.99 (4H4+6, m), 4.30-3.91 (4H8+10, AA'BB'); ^{13}C NMR δ 189.3 (C1, dd, ^{1}J=181.3, ^{3}J=3.7), 160.9 (C7, s), 135.7 (C5, dd, ^{1}J=159.1, ^{3}J=9.2), 128.0 (C3, dd, ^{1}J=161.8, ^{3}J=8.3), 124.9 (C2, s), 120.8 (C4, dd, ^{1}J=162.8, ^{3}J=7.4), 112.8 (C6, dd, ^{1}J=159.1, ^{3}J=7.4), 69.6 (C10, t, ^{1}J=145.2), 68.1 (C8, t, ^{1}J=124.4); IR (KBr) 2940, 2780, 1670, 1590, 1390, 1050, 750 cm^{-1}; UV (MeOH) λ(ε) 214 (146000), 252 (76400), 318 (62000) nm; MS *m/e* 316 (M+2, 0.3), 315 (M+1, 1.3), 314 (M^+, 5.9), 165 (5.6), 149 (42.0), 121 (100); Analysis ($C_{18}H_{18}O_5$) calculated : 68.78 % C, 5.77 % H. Found : 68.55 % C, 5.95 % H.

2,2'-[Oxybis(2,1-ethanediyloxy)]bisacetophenone (4m) : A solution of 10.9 g (80 mmol) of 2-hydroxyacetophenone in 50 mL of THF was added to a refluxing suspension of 3.36 g

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(84 mmol) of NaOH in 50 mL of HMPA and refluxed until dissolution was achieved (50 min). Then, a solution of 10.0 g (38.2 mmol) of diethylene glycol dimesylate[113] in 50 mL of THF was added dropwise over 30 min and the mixture refluxed for 3 h, cooled to 25°C, and filtered. The filtrate was diluted with 250 mL of H_2O and extracted with 3x100 mL of Et_2O. The combined organic extract was washed with successively 3x50 mL of 5 % KOH and 100 mL of brine, dried over Na_2SO_4 and concentrated *in vacuo* to yield (89.0 %) 11.6 g of a yellowish powder: MP 69.5-70°C.

^1H NMR δ 7.71 (2 H3, dd, J_1=7.8, J_2=1.5), 7.41 (2 H5, td, J_1=7.8, J_2=2.0), 6.96 (4H4+6, m), 4.07 (8H8+10, AA'BB'), 2.60 (6H9, s); ^{13}C NMR δ 199.673(C1, s), 157.96 (C7, s), 133.56 (C5, d, ^1J=167.8), 130.37 (C3, d, ^1J=152.6), 128.55 (C2, s), 120.92 (C4, d, ^1J=162.3), 112.61 (C6, d, ^1J=158.4), 69.68 (C10, t, ^1J=142.5), 67.85 (C8, t, ^1J=145.3), 31.83 (C9, q, ^1J=128.3); IR (KBr) 3072, 2942, 2910, 1665, 1596, 1580, 1480, 1447, 1417, 1358, 1295, 1240, 1164, 1120, 1082, 1065, 1047, 950, 940, 756 cm^{-1}; UV (MeOH) λ(ε) 305 (6780), 246 (14400), 212 (37700) nm; MS *m/e* 342 (M^+, 0.6), 207 (18.6), 164 (10.8), 163 (100), 162 (30.4), 150 (18), 149 (40.7), 147 (24.4), 136 (73), 135 (25.5), 121 (73.8), 120 (15.4), 119 (40.3), 115 (14.1), 107 (84.1), 105 (11.6), 95 (13.2), 92 (21.7), 91 (85.9), 87 (15.5), 77 (30), 65 (17.9), 43 (24.4).

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2,2'-(1,5-Pentanediyloxy)bisbenzaldehyde (5h) : A solution of 5.0 g (41 mmol) of salicylaldehyde in 20 mL of dioxane was added to a refluxing suspension of 1.84 g (45 mmol) of NaOH in 20 mL of HMPA and refluxed until dissolution was achieved. A solution of 5.23 g (22.8 mmol) of 1,5-dibromopentane (MCB) in 20 mL of dioxane was then added dropwise. The resulting heterogeneous mixture was refluxed for 3 h, cooled to 25°C, and filtered. The filtrate was diluted with 100 mL of H_2O, and extracted with 3x50 mL of Et_2O. The combined organic extract was washed with 2x25 mL of 5% KOH and 50 mL of brine, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting orange oil was redissolved in 125 mL of Et_2O, washed with 2x25 mL of 5% KOH and 50 mL of brine, dried over Na_2SO_4 , clarified with charcoal, and concentrated *in vacuo* obtaining (96.5 %) 6.16 g of a white powder: MP 50.5-53.0°C(Et_2O), 61-65°C(MeOH), Lit.[101] MP 66-66.5°C(MeOH).

^{1}H NMR δ 10.47 (2H1, s), 7.79 (2H3, dd, J_1=7.8, J_2=1.8), 7.49 (2H5, td, J_1=7.9, J_2=1.8,), 6.97 (4H4+6, m), 4.09 (4H8, ca t), 1.90 (4H10, ca q), 1.70 (2H11, m); ^{13}C NMR δ 189.46 (C1, d, ^{1}J=176.1), 152.38 (C7, s), 135.77 (C5, dd, ^{1}J=159.8, ^{3}J=8.2), 128.41 (C3, dd, ^{1}J=162.1, ^{3}J=8.3), 125.18 (C2, s), 120.70 (C4, dd, ^{1}J=162.7, ^{3}J=7.3), 112.61 (C6, dd, ^{1}J=159.2, ^{3}J=8.3), 68.36 (C8, t, ^{1}J=139.2), 28.87 (C10, t, ^{1}J=133.0), 22.79 (C11, t, ^{1}J= 125.3); IR (KBr) 3080, 3052, 2945, 2913, 2860, 1675, 1598, 1463, 1390, 1290, 1237, 1192, 1160, 1049,

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1036, 1018, 842, 755 cm^{-1}; UV(MeOH) $\lambda(\epsilon)$ 319 (6270), 253 (14600), 214 (32700) nm; MS *m/e* 272 (6.9), 270 (7.1), 149 (17.7), 131 (12.5), 122 (85.9), 121 (100), 104 (11), 94 (7.9), 93 (8.5), 85 (9.6), 77 (13), 69 (34.2), 65 (11.3), 41 (9.1).

2,2'-[1,2-Benzenediyl<u>bis</u>(methoxy)]<u>bis</u>benzaldehyde (6h) : A solution of 47.4 g (0.39 mol) of salicylaldehyde in 90 mL of THF was added in one portion to a suspension of 16.2 g (0.4 mol) of NaOH in 90 mL of HMPA and refluxed for 30 min (no dissolution was observed). Then, a solution of 46.6 g (0.18 mol) of 1,2-dibromomethyl benzene (Aldrich) in 90 mL of THF was added dropwise. The reflux was continued for 3 h, after which the reaction mixture was allowed to reach 25°C and filtered. The filtrate was diluted with 250 mL of H_2O and extracted with three 150 mL portions of Et_2O. The combined organic extract was washed with 2x50 mL of 5% KOH and 100 mL of brine, dried over Na_2SO_4, concentrated under vacuum to half of its volume and filtered to yield (76.0 %) 46.4 g of a white crystalline product: MP 113.5-115.0°C. ^1H NMR δ 10.42 (2H1, s), 7.78 (2H3, dd, J_1=7.8, J_2=1.8), 7.47 (6H5+11, m), 7.00 (4H4+6, m), 5.30 (4H8, s); ^{13}C NMR δ 188.74 (C1, dd, ^1J=179.4, ^3J=3.7), 160.24 (C7, s), 135.62 (C5, dd, ^1J=157.2, ^3J=9.3), 134.00 (C10, s), 128.71 (C3, dd, ^1J=157.2, ^3J=7.4), 128.46 (C11, dd, ^1J=161.8, ^3J=8.3), 124.79 (C2, dd, ^2J=29.6, ^3J=5.6), 120.81 (C4, dd, ^1J=162.8, ^3J= 7.4), 112.61 (C6, dd, ^1J=157.2, ^3J=9.3), 68.16 (C8, t,

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^1J=144.3); IR (KBr) 3075, 3055, 2864, 1680, 1603, 1489, 1462, 1449, 1400, 1388, 1292, 1240, 1192, 1167, 1105, 1048, 1002, 760 cm^{-1}; UV (MeOH) $\lambda(\epsilon)$ 317 (7210), 253 (15800), 215 (46000) nm; MS *m/e* 225 (22.9), 224 (41.6), 206 (13.6), 197 (41.1), 179 (21.2), 169 (11.2), 141 (12.2), 129 (16.9), 105 (100), 104 (47.9), 103 (32.7), 91 (27), 78 (25.8), 77 (16.2), 65 (16.4).

(*E*)- and (*Z*)-**6,7,9,10-Tetrahydrodibenzo-[*h*,*l*][1,4,7]tri-***oxacyclotridecin* (*E*- and *Z*-**7h**) : Under an argon atmosphere, 854 mg (4.5 mmol) of $TiCl_4$ were added *via* syringe to a suspension of 588 mg (9 mmol) of Zn dust in 15 mL of dioxane. This mixture was stirred for 1 h at 25°C, after which a solution of 471 mg (1.5 mmol) of **4h** in 5 mL of dioxane was added dropwise (2.7 h). The resulting dark suspension was stirred for 1 hr, refluxed for 6.3 h, and allowed to cool down to 25°C. The resulting black suspension was then diluted with 25 mL of 10% K_2CO_3, stirred overnight open to the atmosphere, and filtered. The filtrate was extracted with 10x15 mL portions of Et_2O, the combined organic extract was washed with 25 mL of 5% $NaHSO_3$ and 25 mL of brine, dried over Na_2SO_4 and concentrated *in vacuo* to yield 349 mg of a mixture of both isomers as an off-white oil (82.5% yield, 60/40 *E/Z* by NMR). Most of the *E*- isomer could be separated by fractional recrystallization from cyclohexane. The *Z*- isomer had to be purified by PTLC (silica gel, 20 % CH_2Cl_2 in hexane, v/v).

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E-**7h** : MP 149.5-150.5°C; ^{1}H NMR δ 7.80 (2H1, s), 7.47 (2H3, dd, J_1=7.3, J_2=1.8), 7.15 (2H5, td, J_1=7.3, J_2=1.8), 7.04-6.93 (4H4+6, m), 4.14-4.10 (4H8, AA'BB'/2), 3.87-3.83 (4H10, AA'BB'/2); ^{13}C NMR δ 157.23 (C7, s), 129.30 (C2, s), 127.86 (C3, dd, ^{1}J=160.9, ^{3}J=7.4), 127.39 (C5, dd, ^{1}J=160.9, ^{3}J=7.4), 126.47 (C1, d, ^{1}J=157.2), 122.50 (C4, dd, ^{1}J=156.0, ^{3}J=8.3), 117.24 (C6, dd, ^{1}J=158.1, ^{3}J=8.3), 70.75 (C10, t, ^{1}J=142.4), 70.09 (C8, t, ^{1}J=143.2); IR (KBr) 3020, 1640, 1590, 1470, 1445, 1250, 1030, 990 cm^{-1}; UV (MeOH) λ(ε) 207 (24900), 232 (14600), 237 (sh,14100), 289 (15300), 300 (15600), 320 (19100), 334 (sh,13800) nm; MS *m/e* 284 (M+2, 3.1), 283 (M+1, 15), 282 (M$^+$, 100), 223 (15.5), 131 (14.7), 165 (9.6), 181 (10.5).

Z-**7h** : MP 102.0-103.0°C; ^{1}H NMR δ 7.14-6.67 (8H3+4+5+6, m), 6.66 (2H1, s), 4.04-3.74 (8H8+10, m); ^{13}C NMR δ 155.45 (C7, s), 132.27 (C2, s), 129.97 (C3, dd, ^{1}J=140.6, ^{3}J=9.3), 127.78 (C5, dd, ^{1}J=160.9, ^{3}J=9.3), 127.40 (C1, d, ^{1}J=160.9), 115.12 (C4, dd, ^{1}J=140.6, ^{3}J=9.3), 113.68 (C6, dd, ^{1}J=157.2, ^{3}J=7.4), 70.75 (C10, t, ^{1}J=142.4), 68.91 (C8, t, ^{1}J=135.0); IR (nujol mull) 2860, 1600, 1490, 1250, 1150, 1055, 950 cm^{-1}; UV(MeOH) λ(ε) 216 (sh, 26800), 272 (6700), 279 (6700) nm; MS *m/e* 283 (M+1, 18), 282 (M$^+$, 100), 223 (25.2).

(*E*)- and (*Z*)-6,7,9,10-Tetrahydrodibenzo-[*h*,*l*]-10,11-dimethyl[1,4,7]trioxacyclotridecin (*E*- and *Z*-**7m**) : Under argon atmosphere, 8.32 g (45 mmol) of neat $TiCl_4$ were added

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to a cooled suspension of 5.73 g (90 mmol) of Zn dust in 150 mL of dioxane and the mixture was refluxed for 1 h. Then, a solution of 5.0 g (15 mmol) of **4m** in 50 mL of dioxane was added dropwise over 8.5 h, and the reflux continued for 16 h. The reaction mixture was cooled to 25°C, diluted with 200 mL of 10% K_2CO_3 and stirred open to the atmosphere for 3 h, when total oxidation of the titanium was completed as evidenced by the off-white color. The suspension was then filtered, and the filtrate extracted with 3x300 mL of ether. The combined organic extract was washed with 2x50 mL of brine, dried over Na_2SO_4 and concentrated *in vacuo* to yield (81.9 %) 3.712 g of a mixture of both isomers as a yellowish oil (59/41 *Z/E* by NMR). The isomers could be separated by PTLC (silica gel, 7.5 % acetone in hexane, v/v).

E-**7m** : MP 71-72.5°C; ^{1}H NMR δ 7.27-7.17 (4H3+5, m), 7.06-6.95 (4H4+6, m), 4.16-4.08 (4H8, m), 3.96-3.81 (4H10, m), 1.75 (6H9, s); ^{13}C NMR δ 156.34 (C7, s), 135.36 (C2, s), 130.47 (C1, s), 129.67 (C3, d), 127.66 (C5, d), 121.87 (C4, d), 115.84 (C6, d), 70.79 (C10, t), 70.61 (C8, t), 21.54 (C9, q) ; IR (KBr) 2918, 2868, 1598, 1582, 1487, 1445, 1263, 1143, 1085, 1061, 1032, 943, 913, 841, 753 cm^{-1} ; UV(MeOH) λ(ε) 278 (3400), 274 (3600), 208 (26500) nm; MS *m/e* 312 (M+2, 3.3), 311 (M+1, 21.3), 310 (M^+, 100), 251 (12.4), 237 (14.3), 223 (24.2), 178 (14.3), 165 (13.2), 147 (16.2), 146 (15.7), 145 (36.1), 133 (10.9), 132 (11.4), 131

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(18.4), 121 (13.2), 119 (13.4), 115 (11.9), 107 (10.8), 91 (22.7), 77 (12.5).

Z-**7m** : MP 93.0-94.0°C; ^{1}H NMR δ 6.95 (2H3, ca.td), 6.67 (6H4+5+6, m), 3.91 (8H8+10, m), 2.10 (6H9, s); ^{13}C NMR δ 155.50 (C7, s), 134.52 (C2, s), 131.00 (C3, dd, ^{1}J=158.1, ^{3}J=8.3), 130.58 (C1, s), 126.76 (C5, dd, ^{1}J=160.9, ^{3}J=9.3), 120.09 (C5, dd, ^{1}J=160.9, ^{3}J=7.4), 113.59 (C5, dd, ^{1}J=157.2, ^{3}J=7.4), 69.87 (C10, t, ^{1}J=142.4), 68.44 (C8, t, ^{1}J=146.1), 20.28 (C9, q, ^{1}J=127.6); IR (KBr) 3062, 3027, 2968, 2950, 2930, 2903, 1598, 1582, 1485, 1461, 1442, 1401, 1380, 1244, 1213, 1139, 1128, 1100, 1062, 1044, 910, 835, 749 cm^{-1}; UV (MeOH) λ(ε) 288 (br, 5030), 210 (sh, 24600) nm; MS *m/e* 312 (M+2, 4.5), 311 (M+1, 22.4), 310 (M^{+}, 100), 295 (10.1), 251 (19.2), 237 (15.2), 237 (15.2), 223 (32.4), 178 (24.7), 165 (26.7), 152 (20), 146 (27.2), 133 (20.3), 131 (40.2), 119 (34.9); Analysis ($C_{20}H_{22}O_3$), calculated : 77.39 % C, 7.14 % H. Found : 77.26 % C, 7.26 % H.

(*E*)- and (*Z*)-**6,7,9,10-Tetrahydrodibenzo-[*h*,*l*][1,7]-dioxacyclotridecin** (*E*- and *Z*-**8h**) : Under argon atmosphere 8.54 g (45 mmol) of $TiCl_4$ were added at once to a suspension of 5.72 g (90 mmol) of Zn dust in 13 mL of dioxane at 25°C. The mixture was refluxed for 1 h and a solution of 4.68 g (15 mmol) of **5h** in 45 mL of dioxane was added over 15 min . The mixture was refluxed 16 h, cooled to 25°C, quenched with 225 mL of 10 % K_2CO_3 and stirred 4 h open to the atmosphere.

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The resulting yellowish suspension was filtered, the solid was extracted with 50 mL of ether, and the filtrate was extracted with 4x70 mL of Et_2O. The combined organic extract was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to a third of its original volume, when extensive crystallization was observed. The liquor was decanted, concentrated to half volume and decanted again. The solid obtained was pure *E*- isomer. The supernatant was then dried and analyzed. It was a mixture of isomers (89/11 *Z/E* by NMR). After complete evaporation of the solvent, the *E*-isomer crystallized of this mixture leaving pure *Z*, as a supernatant. Total yield: 2.67 g (63.5 %), 62/38 *Z/E*). The *Z*- isomer was purified by PTLC (silica gel, Et_2O: pet. ether 1:2 v/v).

E-**8h** : MP 140-141°C; ^{1}H NMR δ 7.69 (2H1, s), 7.47 (2H3, dd, J_1=7.6, J_2=2.0), 7.16 (2H5, ddd, J_1=7.8, J_2=7.3, J_3=2.0), 6.99 (2H4, ddd, J_1=7.6, J_2=7.3, J_3=1.5), 6.95 (2H6, dd, J_1=7.8, J_2=1.5,), 4.01 (4H8, t, J= 5.9), 2.05 (2H10, m), 1.85 (4H10, q, J_1=5.9, J_2=5.4); ^{13}C NMR δ 157.63 (C7, s), 128.89 (C2, s), 127.97 (C5, dd, ^{1}J=160.9, ^{3}J=9.3), 127.81 (C3, dd, ^{1}J=160.9, ^{3}J=7.4), 126.49 (C1, d, ^{1}J=157.2), 122.13 (C4, dd, ^{1}J=159.1, ^{3}J=7.4), 116.92 (C6, dd, ^{1}J= 158.1, ^{3}J=8.3), 70.13 (C8, t, ^{1}J=143.3), 28.97 (C10, t, ^{1}J=126.7), 20.92 (C11, t, ^{1}J=116.5); IR (KBr) 3064, 3030, 2940, 2915, 2870, 1596, 1576, 1481, 1472, 1457, 1432, 1382, 1335, 1260, 1229, 1122, 1091, 1043, 1012,987, 943, 884, 758 cm^{-1} ; UV

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(MeOH) λ(ε) 335 (sh, 15900), 321 (21800), 299 (16900), 288 (16900), 233 (148000), 209 (22600) nm; MS *m/e* 282 (M+2, 3.1), 281 (M+1, 19.7), 280 (M^+, 100), 223 (16.4) , 212 (18.7), 211 (16.4), 210 (20.3), 195 (12.9), 183 (15.3), 181 (32.8), 173 (14.4), 165 (44.8), 153 (14.8), 152 (25), 145 (17.9), 133 (17.7), 131 (51.6), 119 (28.1), 107 (39.8), 91 (16), 77 (13.2), 69 (15), 41 (14.7).

Z-**8h** : oil, decomposes on attempted distillation; ^{1}H NMR δ 6.95 (4H3+5, m), 6.66 (2H1, s), 6.64 (4H4+6, m), 3.81 (4H8, br t, Japp=4.9), 1.65 (2H11, br), 1.43 (4H10, br q, Japp=5.9); ^{13}C NMR δ 155.76 (C7, s), 130.73 (C3, dd, ^{1}J=146.9, ^{3}J=8.8), 128.26 (C1, d, ^{1}J=159.1), 127.76 (C5, dd, ^{1}J=147.6, ^{3}J=9.1), 126.62 (C2, s), 120.47 (C4, dd, ^{1}J=162.2, ^{3}J=7.7), 114.64 (C6, dd, ^{1}J=158.0, ^{3}J=8.0), 67.77 (C8, t, ^{1}J=142.4), 27.06 (C10, t, ^{1}J=123.0), 21.02 (C11, t, ^{1}J=120.0); IR (Neat) 3063, 3020, 2930, 2880, 1598, 1579, 1483, 1450, 1390, 1248, 1210, 1158, 1106, 1043, 943, 748 cm^{-1}; UV (MeOH) λ(ε) 282 (br, 4820), 210 (20000) nm; MS *m/e* 282 (M+2, 3.1), 281 (M+1, 20.3), 280 (M^+, 100), 223 (17.5), 212 (20.1), 211 (16.4), 210 (22.7), 195 (15.7), 183 (17.3), 181 (37.7), 173 (16.2), 166 (10.8), 165 (56.3), 164 (12.2), 153 (17.8), 152 (30.7), 145 (21.2), 144 (10.7), 133 (21), 131 (60.8), 120 (10.8), 119 (28.5), 118 (22.7), 115 (14.9), 107 (48.4), 91 (20.6), 77 (16.4), 69 (14.1), 41 (16.6).

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(*E*)-2,2'-Ethenediylbisphenol (*E*-9h) : Under argon atmosphere, 8.54 g (45 mmol) $TiCl_4$ were added to a suspension of 5.88 g (90 mmol) of Zn dust in 120 mL of dioxane. The mixture was refluxed 40 min, and a solution of 5.19 g (15 mmol) of **6h** in 45 mL of dioxane was added dropwise over 1 h. Reflux was continued for 3.5 h. The mixture was cooled to 25°C and diluted with 200 mL of 10% aq K_2CO_3, stirred overnight, and filtered. The filtrate was extracted with 3x150 mL of CH_2Cl_2. The organic phase was then washed with 100 mL brine, dried over Na_2SO_4 and concentrated *in vacuo*, obtaining a very viscous oil. Trituration with $CHCl_3$ afforded (73.8 %) 2.35 g of the product as very small colorless crystals.

MP 194.5-195.5°C (Lit.[114] MP 197°C); ^1H NMR ($CDCl_3$-$(CD_3)_2CO$) δ 8.41 (2HO-H, br s), 7.59 (2H3, d, J=7.9), 7.54 (2H1, s), 7.06 (2H5, m), 6.86 (4H4+6, m); ^{13}C NMR [$(CD_3)_2CO$] δ 155.62 (C7, s), 129.04 (C3, d, ^1J=160.1), 127.23 (C5, d, ^1J=160.3), 126.28 (C2, s), 124.36 (C2, d, ^1J=157.9), 120.78 (C4, d, ^1J=160.5), 116.75 (C6, d, ^1J=157.8); IR (KBr) 3342, 3230, 3045, 1605, 1585, 1500, 1450, 1369, 1333, 1200, 1155, 1090, 1042, 982, 972, 855, 751, 739, 595, 586 cm^{-1}; UV (MeOH) λ(ε) 331 (19800), 280 (13700), 234 (13200), 211 (23600) nm; MS *m/e* 214 (M+2, 1.7), 213 (M+1, 15.2), 212 (M^+, 100), 211 (23.4), 197 (11.8), 195 (27.2), 183 (13.3), 181 (9.6), 165 (27), 152 (9.8), 118 (9.6), 91 (7.6), 82 (11.3), 77 (11.3).

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CHAPTER IV. Progress Towards the Synthesis of the Functionalized Stilbene Cycle Model 1.

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IV.1. INTRODUCTION. In the course of the synthesis of the unsubstituted stilbene cycles described in the preceding chapter, it was shown that the low-valent titanium induced condensation of carbonyls could be successfully utilized to form an olefinic bond in a cyclic stilbene system. A new synthetic method to prepare aromatic-aliphatic ethers with both high yields and a convenient isolation procedure was developed. The next phase of research was to combine these procedures with other synthetic methods to prepare the functionalized stilbene 1.

In order to utilize the titanium reaction to prepare a functionalized stilbene-containing ring, a *bis*(2,6-disubstituted)benzaldehyde ether, 3, must first be prepared (see Figure 13 in Chapter I for the synthetic scheme). The simplest route into vicinally disubstituted benzaldehydes is *via* ortho-lithiation of suitable 1,3-disubstituted benzenes, followed by acylation with *N,N*-dimethylformamide (DMF). Given that both substituents already present on the aromatic ring are good "directors" (electron donor ligands) very high yields and regioselectivities of the overall reaction can be obtained.[73] However, the high basicities and nucleophilicities of organolithiums cause the greatest limitations in their application. Because of the high reactivity of both the primary organolithium reagents and the intermediate aryllithiums, protection of any other possible reactive sites in the substrate molecule is required.

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The first necessary step in this synthesis is, therefore, finding adequate methods for the protection of the different m-substituted phenols. In most cases, fortunately, there are protecting groups available that are both compatible with the lithium-hydrogen exchange reaction and good directing groups for it. Tetrahydropyranyl (THP) ethers[115] and methoxymethyl (MOM) ethers[116] for alcohols, and oxazolines for carboxylic acids[117] are probably the better known examples possessing the desired properties. One of the aromatic rings in the *bis*(benzaldehyde) ether 3 precursor to the final stilbene model 1, must carry a functional group that can be later transformed into a carboxylate. It is this functional group that offers the greater problems in the protecting-deprotecting scheme.

The choices in protecting groups that can be utilized to mask this carboxylate are quite limited. It cannot have a free carbonyl that would compete with the aldehyde in the titanium induced cyclization. This excludes the possibility of using a sterically hindered ester or amide, although these groups have been proved to be effective directors for ortho-lithiations.[118] Furthermore, the use of an oxazoline is precluded by its difficulty or preparation and cumbersome removal sequence.[119] At this point, since it is evident that the protecting group utilized can not be at the carboxylic acid oxidation level, a protected aldehyde seems to be the most expedient choice for the masked-carboxylate carrying benzaldehyde.

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For aldehydes, however, there are not many "activating" protecting groups available. Free aldehydes undergo addition of organolithiums at very fast rates, and there are only very sporadic reports of attempts to use aldehyde derivatives in ortho-lithiations. The most common protecting groups for aldehydes are the acetals. However, benzaldehyde acetals have not been used widely as directing groups in lithiations. Only very recently, Rodrigo and coworkers[120] have reported that dimethyl acetals were both effective directors and easily removed protecting groups for benzaldehydes. Once a free aldehyde is obtained by acid hydrolysis of its acetal, it can be easily and selectively transformed to a carboxylic acid by silver oxide[121] or cyanide-promoted manganese dioxide oxidation.[122] An acetal-protected aldehyde is, for these reasons, the first choice for the carboxylate group precursor.

IV.2. RESULTS AND DISCUSSION. In an attempt to obtain the dioxolane acetal of 3-hydroxybenzaldehyde, the phenolic aldehyde was treated with ethylene glycol and a catalytic amount of *p*-toluenesulfonic acid. After refluxing the mixture for 48 hours no product could be detected. Several variants of this method (using a soxhlet packed with molecular sieves; adding trimethyl orthoformate, as a water scavenger; Dean-Stark separation of the azeotropically distilled water), were also attempted with equally unsuccessful results.

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IV.2.1. Synthesis of Dimethyl Acetal Precursors to 1.

a) *Bis*(aryl) ethers.

The lack of reactivity of phenolic aldehydes towards acetalization was known for some time. As early as 1898, Fischer reported[123] that phenolic aldehydes did not undergo acid-catalized acetalizations readily. The common way around this difficulty was to block the phenolic hydroxyl with an acetate or other acid-stable, base-labile derivative followed by acetalization and alkaline hydrolysis of the phenolic blocking group.[124],[125] This was both cumbersome and low yielding, so an alternative method of acetal synthesis which could be used to form phenolic acetals was needed. The most attractive way found in the literature seemed to be that by Kantlehner,[126] in which a dimethylformamide-dimethyl sulfate addition complex[127] is used both as an acid and water scavenger. When methanol, water, and 3-hydroxybenzaldehyde were treated with the dimethylformamide-dimethyl sulfate complex (DD) according to this procedure,[126] the dimethyl acetal 10a was obtained (85 %) in one step. Although this material is pure by NMR, it was found to be impossible to further purify an analytical sample because of its unstability. It decomposed on attempted vacuum distillation or chromatography on silica gel. This unstability was later found to be a common property of all the dimethyl acetals prepared in this work.

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The precursor to the other aromatic ring was initially chosen as 3-methoxyphenol since it was commercially available and it provided an easy way to test the subsequent reactions. Even though the methoxy group would not be very easy to remove, the accessibility of the precursor made it attractive as a fast way to synthesize a model necessary to test the reactions. When the anion of 3-methoxyphenol, generated by treatment with NaOH in HMPA-THF, was allowed to react with 2-(2-chloroethoxy)ethanol according to the etherification procedure developed in the preceding chapter, **16a** was obtained in a moderate yield (40 %), but since both starting materials are commercially available, this was not an insurmountable problem. Next, the primary alcohol in the newly generated diethylene glycol monoaryl ether **16a** was tosylated in pyridine-methylene chloride in 93.2 % yield, and the resulting tosylate, **17a**, was treated with the phenoxide obtained by the treatment of **10a** with NaOH in THF-HMPA. The resulting ether, **18a** (81 %), (69 % overall from 3-hydroxybenzaldehyde) was then the first plausible model in which to test the feasibility of the proposed dilithiation-diformylation.

Unfortunately, after innumerable variations in both solvent and temperature were tested by running the reaction on a small scale, adding the electrophile and analyzing the reaction mixtures by NMR; no totally successful dilithiation was observed. At moderately low temperatures (-30 to -10°C)

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the dioxygenated ring could be metallated smoothly in almost 3 hours in the presence of complexing solvents like ethyl ether or THF. Under these conditions, however, the benzaldehyde-acetal-bearing ring was completely unaffected. Addition of *N,N,N,N*-tetramethylethylene diamine[128] (TMEDA) or hexamethylphosphorictriamide (HMPA) to attempt promoting the reaction proved to be completely ineffective.

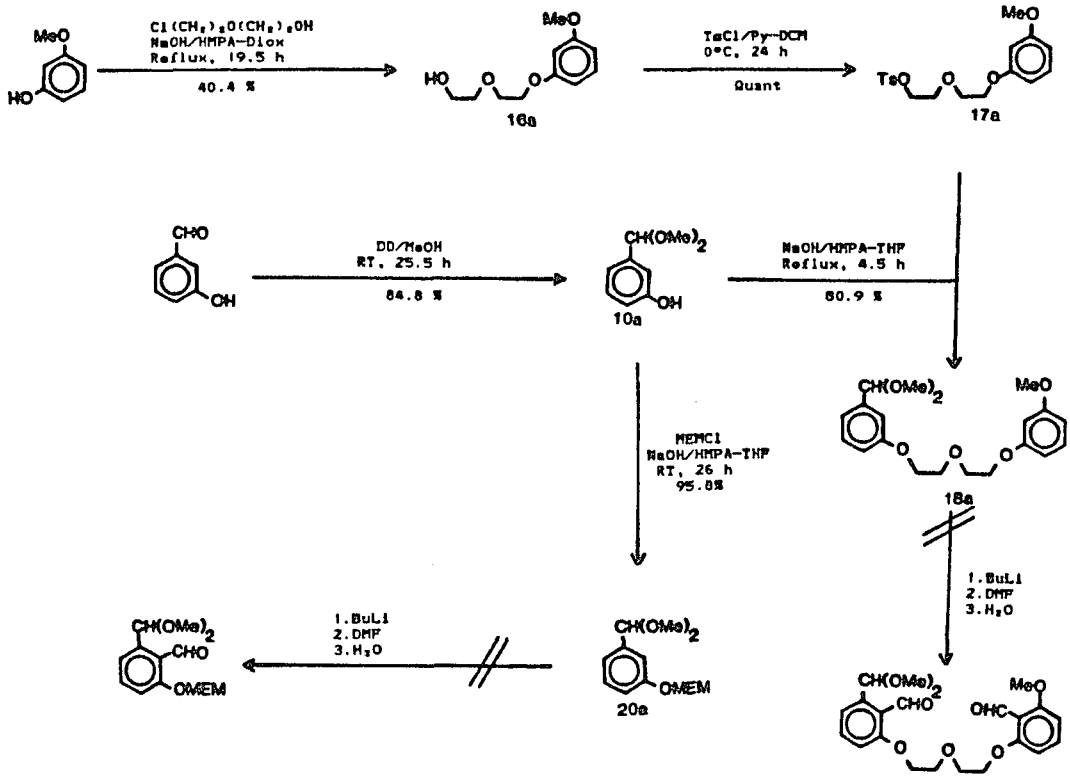

Figure 21. Synthesis of dimethyl acetal intermediates.

Contrary to the accepted[73] trend that breaking the alkyllithium aggregates by using complexing agents and/or

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oxygenated solvents should increase the effectiveness of the reaction, slightly better results were obtained when hydrocarbon solvents and higher temperatures were used. In the best result of all our experiments, it was found that the methoxy-substituted ring was reacting very rapidly with butyllithium at 0°C in hexane-xylene solvent, being completely metallated in *ca.* 30 minutes, and then decaying slowly, while the acetalic ring was being metallated only very slowly. It was estimated that only between 5 and 10 % dimetallation could be obtained before considerable decomposition of the dioxygenated-ring aryllithium moiety occurred.

b) Mono(aryl) ethers.

To determine if the relatively low directing ability of the dimethyl acetal was the cause of the poor metallation, or the presence of an additional lithiated ring in the dilithiation was in some way hindering it, a derivative of **10a** in which the phenolic hydroxyl was protected had to be synthesized. The MEM (methoxyethoxymethoxy, 2,5-dioxahexyloxy) ether first introduced by Corey[129] was chosen due to the reported ease of its selective removal by $ZnBr_2$ treatment, even in the presence of other acetalic protecting groups,[129] its structural similarity with the diethylene glycol chain in **18a**, and the commercial availability of the required reagent. When **10a** was treated with MEM chloride under our standard Williamson conditions (NaOH, THF-HMPA, reflux), no product could be isolated, and some

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fuming was observed when a solution of the electrophile was introduced into the reaction system. This suggested that the commercial MEM chloride could contain some residual HCl used in its preparation. When the amount of sodium hydroxide was increased to two equivalents and the reaction was conducted at 25°C, the diprotected benzene **20a** was obtained (96 %) in 16 hours.

Numerous attempts to lithiate this acetal were made, and despite all efforts, it could not be successfully metallated. Therefore, the acetalic component seemed to be the cause for the failure of the dilithiation-diformylation scheme and it had to be substituted for a more adequate alternative. In a recent publication,[124] Ronald and Winkle reported the successful lithiation of several dioxane acetals with butyllithium in hexane-cyclohexane mixed solvents. Accordingly, the whole synthetic series was repeated using dioxane acetals instead of the dimethyl acetals.

IV.2.2. Synthesis of Dioxane Acetal Precursors to 1.

a) *Bis*(benzaldehyde) ethers.

In order to avoid a protection-deprotection sequence with the phenolic hydroxyl, the DD-promoted acetalization of 3-hydroxybenzaldehyde with 1,3-propanediol was tried using methylene chloride as solvent and only a three-fold excess of the alcohol, to yield (87 %) the desired acetal, **10b**. This acetal was then treated with 2-(2-chloroethoxy)ethanol,

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and sodium hydroxide in dioxane-HMPA to give (50 %) the diethylene glycol monoaryl ether **11b**. The primary alcohol in this compound was then tosylated in pyridine-methylene chloride to yield (91 %) **12b**.

The synthetic scheme described above had an important variation to the one used in the previous (dimethyl acetal) case. Namely, the diethylene glycol bridge was attached to the acetalic ring instead of linking it to the dioxygenated ring, as in the latter. There was a definite reason to introduce this change. Having the electrophile be the acetalic half of the desired diaryl ether allowed for the more convenient testing of different protecting groups in the dioxygenated ring without requiring several steps before obtaining the necessary bisaromatic ether to test the dilithiation. Instead, several different monoprotected phenols could be synthesized and reacted with the monoaryl ethylene glycol tosylate **12b** obtained above.

With this material at hand, it was an appropriate to change the protecting group on the dioxygenated aromatic ring. The methoxy group used in the previously described sequence to protect the phenolic hydroxyl was not the adequate, since its selective removal would be, at best, very difficult.[130] The alternative was to synthesize the *m*-protected phenol with an easily removable protecting group, since no adequate material was commercially available. In their early paper on *o*-metallation of aromatic ethers, Par-

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ham and Anderson[115] reported obtaining the mono-THP ether of resorcinol as a byproduct in the preparation of the diprotected species. A brief attempt to modify their reaction conditions to favor the monoether formation was made, but only mixtures were obtained.

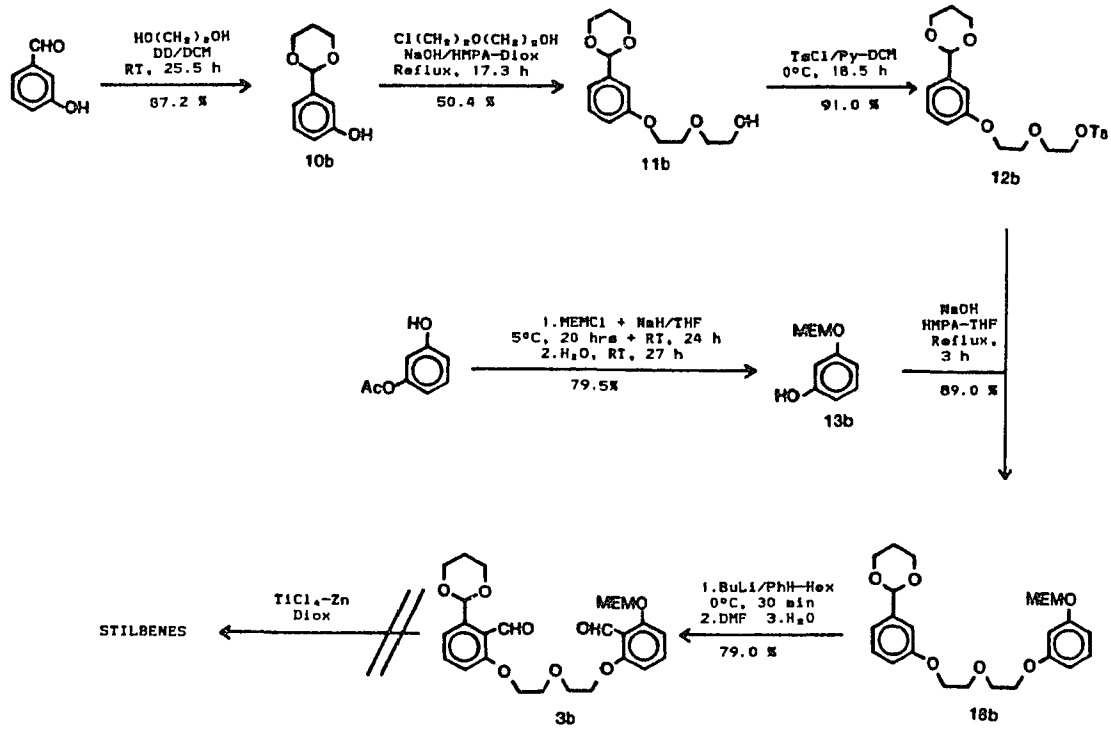

Figure 22. Synthesis of dioxane intermediates.

In light of the successful protection of the dimethyl acetal **10a** phenolic hydroxyl as a MEM ether, a direct monoalkylation of resorcinol with MEM chloride was attempted using our etherification procedure. Only mixtures of starting material, mono- and di-alkylated products were obtained,

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and separation of the desired monoalkylated phenol was impossible. However, when commercially available resorcinol monoacetate was reacted with MEM chloride in THF at 25°C, using sodium hydride as the base, a monoether monoacetate was obtained. This monoacetate was then saponified to yield mono-MEM resorcinol **13b**. When the isolation of the monoacetate intermediate was bypassed, and the reaction mixture from the etherification was carefully diluted with water and stirred overnight at 25°C to saponify the ester, an 80 % yield of product was obtained. This reaction was equally successful in larger scales. This monoprotected phenol was then subjected to typical Williamson conditions with the tosylate **12b** prepared above to yield (89 %) the bisaromatic ether, **18b**.

When **18b** was subjected to the lithiation conditions described by Ronald[124] and subsequently reacted with DMF, only a very low conversion to the dialdehyde **3b** was obtained. Based on the results of the experiments for the dimethyl acetal *bis*(aryl)ether **3a**, the cyclohexane in the mixed solvent was substituted for xylene. A definite, if not completely satisfactory increase in the conversion to the bisbenzaldehyde (*ca* . 25 % could be detected by ^{1}H NMR in the crude reaction mixture) was observed. The solvent composition, temperature, and reaction time were further modified until an optimal combination of 25 % benzene in hexane (v/v) at 0°C for 30 minutes was found. Under these condi-

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tions, **18b** could be cleanly transformed (79 %) *via* dilithiation-diformylation into the desired *bis*(benzaldehyde) **3b**.

b) Mono(benzaldehyde) ethers.

In addition to the bisaromatic ether dilithiation route to the *bis*(benzaldehyde) **3b**, the separate syntheses of both aromatic aldehydes were simultaneously explored. The idea behind these reactions was that, with these compounds available, selective deprotections of the phenols followed by etherifications provided an alternative preparation of the desired *bis*(benzaldehyde) ether.

To obtain the 2,6-dioxygenated benzaldehyde, the free hydroxyl of 2-(2-chloroethoxy)ethanol was protected as a MIP[132] (1-methoxyisopropoxy, 1,1-dimethyl-2-oxapropyloxy) ether by reaction with 2-methoxypropene in ether with catalytic amounts of trichloroacetic acid in a 90 % yield. This chloride was then used to alkylate **13b** under our Williamson conditions to yield (95 %) **15b**. This was considerably higher than expected on the basis of the results obtained with the unprotected alcohol-chloride (40 % in **16a** and 50 % in **11b**), and suggested that the reason for the lower yields in using the free alcohol is the deprotonation of the hydroxyl and nucleophilic displacement of the chloride to form dioxane, rather than the chloride being a poorer leaving group than the tosylates or bromides used in our other alkylations.

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The diprotected benzene **15b** so obtained was then treated, following the results in the dimethyl acetal-methoxy *bis*(aryl) ether **18a**, with butyllithium in ether at -30°C and reacted with DMF to yield (95 %) the monoaldehyde **24b**. The selective removal of the MIP protecting group was, much to our surprise, extremely simple. When, in order

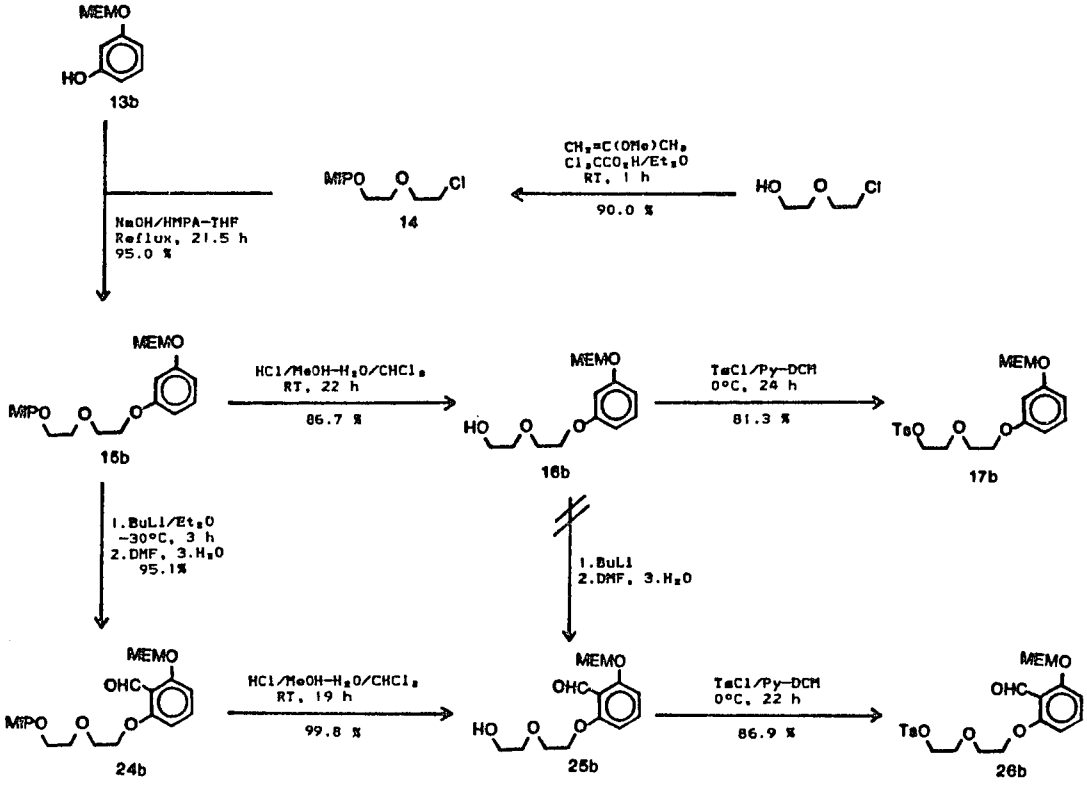

Figure 23. Synthesis of MEM-ether intermediates.

to assess the relative labilities of the MEM and MIP acetalic ethers, a solution of **24b** in $CDCl_3$ was mixed with

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D_2O in a NMR tube, no hydrolysis of either group was observed. On addition of a drop of DCl in D_2O, the slow disappearance of the MIP ether's strong singlet at δ 1.2, with concomitant appearance of sharp singlets characteristic of methanol and acetone was observed. When the reaction was repeated in a larger scale using a biphasic $HCl-H_2O/CHCl_3$ mixture, a practically quantitative (99.8 %) yield of the monoalcohol **25b** was obtained. The hydroxy group in **25b** was tosylated in pyridine-methylene chloride at 0°C to yield (87 %) the tosylate **26b**.

The MIP ether on the non-aldehydic diprotected benzene, **15b**, was selectively removed using the biphasic conditions to yield (87 %) **16b**. This yield compounded to an overall yield from the mono-MEM resorcinol **13b** of 74 %, considerably higher than could be expected to be obtained by the direct reaction of this phenol with 2-(2-chloroethoxy)ethanol, even when two additional reactions were conducted. The direct lithiation of molecules containing aliphatic hydroxyl groups by using an additional equivalent of butyl lithium to generate the alkoxide of the alcohol has been reported.[131] This material was treated with two equivalents of butyllithium, followed by reaction with DMF. After quenching and aqueous work-up, only unchanged starting material was detected by NMR. Clearly, it was convenient to introduce the aldehyde before the aliphatic hydroxyl was deprotected.

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To obtain the benzaldehyde precursor to the benzoic acid half of the model, the phenolic dioxane acetal **10b** was allowed to react with sodium hydroxide and MEM chloride in THF-HMPA at 25°C, obtaining a 96 % yield of the diprotected species, **20b**. This material could be easily lithiated and formylated under the same conditions as the bisaromatic ether **18b** to give (93 %) the monoaldehyde **22b**. The selective deprotection of the phenol while preserving the dioxane acetal was, however, impossible. When Corey's $ZnBr_2$ procedure, acidic methanol or methanol-water, was tried, both protecting groups were removed. When the chloroform-aqueous acid biphasic reaction was tried, only the dioxane acetal was hydrolysed.

In the light of the excellent results obtained using MIP ethers as protecting groups, **10b** was reacted with 2-methoxypropene in ether containing catalytic amounts of

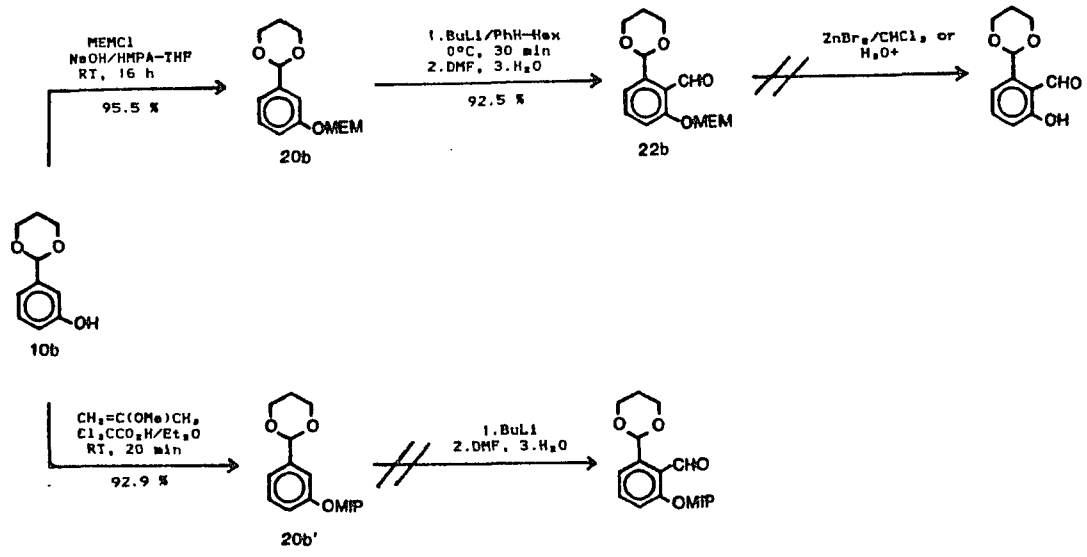

Figure 24. Synthesis of dioxane monoaldehyde intermediates.

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trichloroacetic acid. After aqueous work-up, the diprotected **20b'** was obtained (93 %). As expected, when the biphasic acid hydrolysis of **20b'** was effected in a NMR tube experiment, the MIP protecting group was hydrolysed selectively. However, **20b'** was unreactive towards butyllithium, presumably due to the excessive steric hindrance of the combined protecting groups. The separate monolithiation-monoformylation route was therefore, at least with a dioxane acetal, not applicable to the synthesis of the necessary *bis*(benzaldehyde) **3b**.

c) Attempted cyclization of dioxane *bis*(benzaldehyde) ethers.

The low-valent titanium induced cyclization of the dialdehyde obtained by the dilithiation-diformylation route previously described was quite unsuccessful. A large amount of decomposition was observed, no product could be isolated, and a very complex mixture was obtained. No indications of appreciable amounts of stilbenes could be detected by NMR.

An additional complication found in the use of dioxane acetals as protecting groups for aldehydes was their extreme sensitivity to hydrolysis. Extensive hydrolysis of the acetalic group was noticed when these compounds were isolated using normal aqueous isolation procedures. However, this problem was completely eliminated when the aqueous solutions utilized in their isolation were buffered by addition of sodium acetate to make a 10 % concentration. Similarly to

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the dimethyl acetals, these compounds decomposed on attempted distillation or chromatography to obtain analytical samples.

Since the results of the above experiments indicated that a benzaldehyde acetal would not survive the titanium reaction conditions and in the monolithiation approach it could not be preserved while deprotecting the phenol, it was decided to substitute a benzylic alcohol as the synthon for the desired carboxylic acid. This substitution had several implications for the synthetic scheme. First, a benzyl alcohol could be easily protected as a methyl ether, which is considerably more stable to acidic conditions than an acetal. Thus, it seemed highly probable that it can be preserved while deprotecting a MEM-protected phenol. Second, since benzylic alcohols are considerably less acidic than phenols, the direct etherification of the former without prior blocking of the latter was not very probable. This would introduce additional protection and deprotection reactions in the synthetic sequence. Third, even though a benzylic methylene is one oxidation level further removed from an acid than an acetalized aldehyde, oxidation of similar benzyl ethers have been reported under relatively mild conditions.[133] The whole synthesis had to be repeated using a benzyl ether as the precursor for the carboxylate.

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IV.2.3. Synthesis of benzyl ether precursors to I.

When recrystallized 3-hydroxybenzyl alcohol was reacted with MEM chloride and NaOH in THF-HMPA at 25°C, the MEM-protected benzyl alcohol **19c** was obtained (85 %). This compound could be, in contrast to **16b** above, lithiated in hexane-benzene at 5°C by using two equivalents of butyllithium in 1 hour. Treatment of the aryllithium with DMF followed by aqueous work-up yielded (55 %) the hemiacetal of the expected aldehyde **21c** . Since no literature precedent could be found on the reactions of low-valent titanium with hemiacetals, this product was treated with titanium tetrachloride and zinc in refluxing dioxane. However, no stilbenic product could be detected by NMR analysis of the mixture obtained. The protection of the benzylic alcohol was therefore necessary, both to increase the yield of the aldehyde and avoid the formation of the cyclic hemiacetals.

a) *Bis*(benzaldehyde) ethers.

When the benzylic alcohol **19c** was alkylated by treatment with sodium hydride and methyl iodide in THF, the diprotected benzene **20c** was obtained (98 %). The phenolic hydroxyl in **20c** was then selectively released by $ZnBr_2$ treatment in chloroform to yield (60 %) the phenolic benzyl ether **10c**. However, there were great difficulties in the purification of the product of this reaction. The byproduct of the MEM group hydrolysis, 2-methoxyethanol was not totally eliminated in the aqueous washings, so it had to be

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separated from the product by vacuum distillation. Since the product itself had a low boiling point, some of it likely evaporated in the process causing the relatively poor yield.

In order to circumvent this shortcoming, the transformation sequence was repeated substituting a MOM (methoxymethoxy, 2-oxapropyloxy)[116] group for the MEM ether. Thus, on treating 3-hydroxybenzyl alcohol with chloromethyl methyl ether in NaOH, THF-HMPA, the MOM-benzyl alcohol **19c'** was obtained (86 %). Methylation with sodium hydride and methyl iodide in THF yielded (86 %) the diprotected **20c'**, and the free phenolic benzyl ether **10c** was obtained (98 %) on treatment with hydrochloric acid in methanol-water. Although the yield of the benzylic methylation of the MOM protected phenol was *ca.* 10 % lower, it was more than offset by the higher yield in the phenol deprotection. This latter difference was mainly due to the fact that the methoxymethoxy (MOM) moiety is hydrolysed to methanol and formaldehyde, which were much more easily separated from the product than the 2-methoxyethanol byproduct generated on the hydrolysis of the MEM group.

To prepare the necessary *bis*(aryl) ether the previously synthesized MEM-protected alcohol **16b** was tosylated in pyridine-methylene chloride at 0°C to yield (81 %) **17b**, which was then used to alkylate the phenolic benzyl ether **10c**. Under our etherification conditions, the diprotected bisaromatic ether **18c** was obtained (99.6 %). This material

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was then dilithiated and diformylated in benzene-hexane at 10°C to yield (82 %) the *bis*(benzaldehyde)ether **3c**.

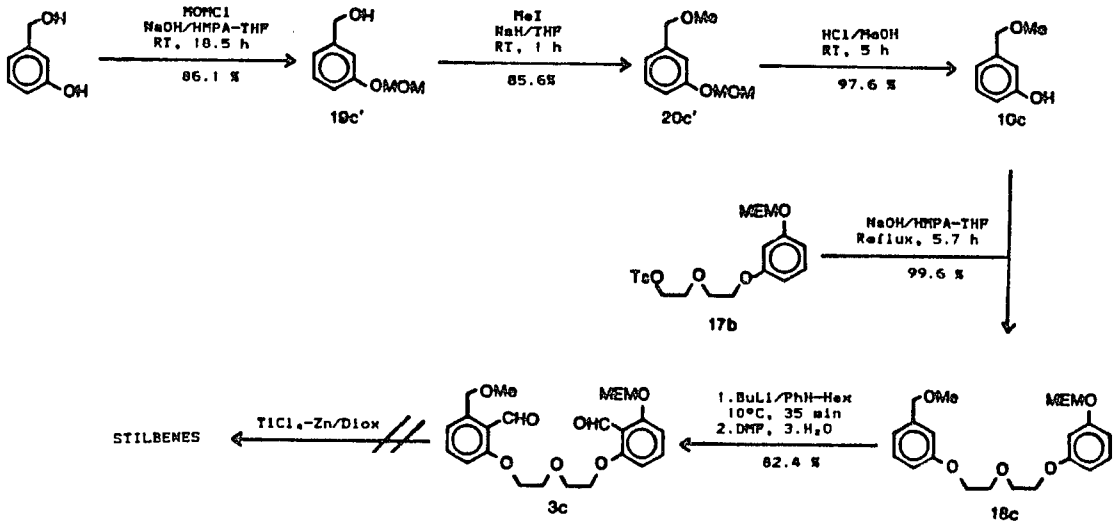

Figure 25. Synthesis of benzyl ether intermediates (I).

b) Mono(benzaldehyde) ethers.

The separate monolithiations-monoformylations to obtain the benzaldehyde precursor to the carboxylic acid also proceeded smoothly using the benzyl ether synthons. The MEM protected ether, **20c**, was transformed into the 2,6-disubstituted benzaldehyde **22c** by lithiation in 25 % benzene in hexane at 10°C for 25 minutes and subsequent reaction with DMF in a 90 % yield. Small amounts (about 2% by NMR) of the isomeric 4-methoxymethylsalicylaldehyde MEM ether were also formed. The free phenol was then obtained by

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treatment of **22c** with $ZnBr_2$ in chloroform to yield (61 %) the substituted salicylaldehyde **23c**.

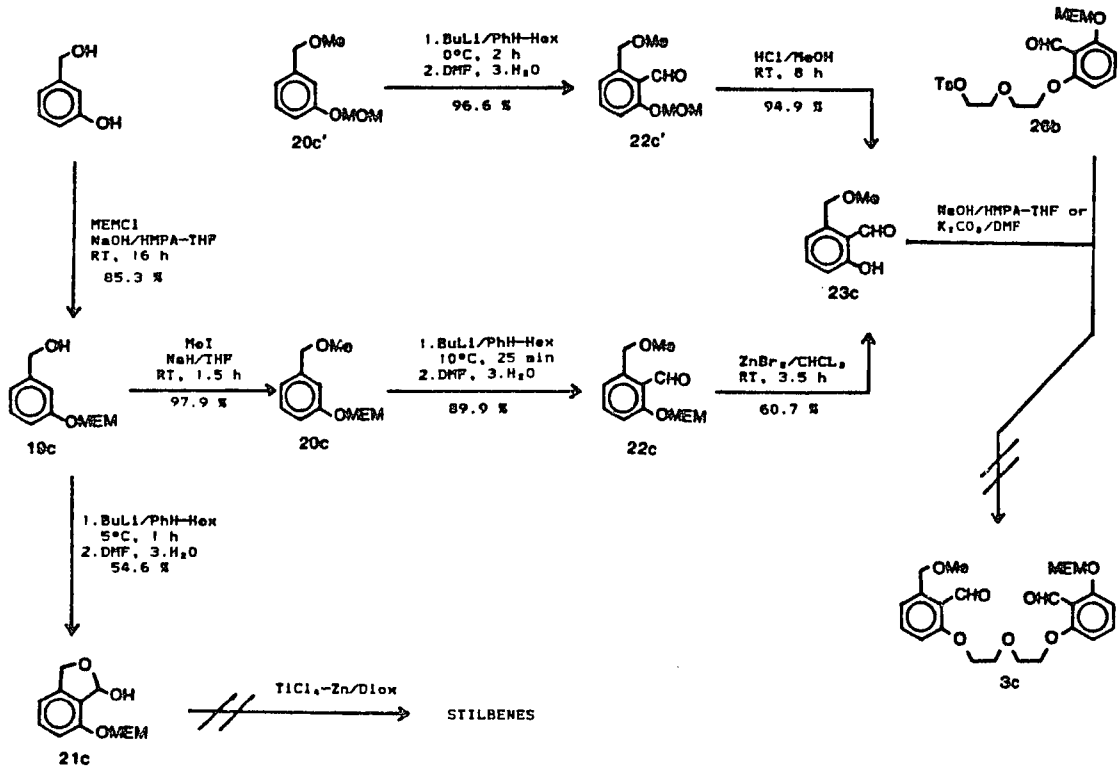

Figure 26. Synthesis of benzyl ether intermediates (II).

On the other hand, the MOM protected benzyl ether **20c'** required a longer reaction time, 2 hours at 0°C, to be completely metallated before addition of the DMF electrophile. Under these conditions a 97 % yield of the MOM protected benzaldehyde **22c'** was obtained, and no isomeric byproducts could be detected by NMR. The deprotection of this product was easily achieved by treatment at 25°C with

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methanolic HCl to yield (95 %) **23c** . Once again, the yield on the deprotection of the MOM ether was considerably higher than its MEM-protected counterpart (61 %), presumably because of the same reason as the non-aldehydic benzyl ethers, **20c** and **20c'**.

A very clear pattern emerged from the results on all the lithiation reactions done in the course of this research. The metallation of strongly activated aromatic rings (the methoxylated ring on **18a** and the MEM protected monoaryl ether **15b**) proceeded smoothly in ethereal solvent, while those substrates which contained weaker directing groups (the dioxane acetal ring in **18b**, the benzylic ether ring in **18c**, and **20b**, **20c**, and **20c'**), reacted better using hydrocarbon solvents. This pattern indicated that in the absence of a strong increase on the acidity of the proton to be abstracted, such as the one caused by having two electron-withdrawing oxygens in the aromatic ring in the first two cases, the complexation of the alkyllithium by the directing groups would play a decisive role in the outcome of the reaction. Therefore, the addition of large amounts of a competing ligand, i.e. ethereal solvents, would inhibit the reaction.

The difference in the regioselectivities obtained in the lithiations of the MEM-protected benzylmethyl ether **20c** (which gave small amounts of the isomeric aldehyde) and its MOM-protected analogue **20c'** (in which no isomeric

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byproducts could be detected, but required considerably longer reaction time) seemed to corroborate this view. Since the electronic effects on the acidity of the different aromatic hydrogens were expected to be very similar on both positions ortho to the oxygen and practically identical between the MEM and the MOM groups, the change of the phenolic protecting group from a MOM (methoxymethoxy) to a better ligand MEM (2-methoxyethoxy)methoxy decreased the effect of the complexation by the benzyl ether, thereby reducing the observed regioselectivity.

When the substituted salicylaldehyde (2-hydroxybenzaldehyde) **23c** was reacted with the tosylate **26b**, no alkylation could be obtained using either our HMPA-THF procedore, NaH in THF, or K_2CO_3 in DMF. However, since the diether can be obtained *via* the more direct dilithiation-diformylation route, this finding did not pose a problem.

c) Attempted cyclization of benzyl ether *bis*(benzaldehyde) ethers.

When the dialdehyde **3c** was subjected to the titanium reaction, though, a very complex mixture was obtained. The downfield portion of the ^1H NMR spectrum was too complex to be able to ascertain the presence of stilbenes, particularly since the vinylic protons were expected to be unequivalent and therefore be coupled to each other. It did reveal, though, that most of the benzylic ether had not been cleaved under the reaction conditions. No appreciable amounts of

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product could be isolated from this mixture by chromatographic methods. On the rationale of minimizing the decomposition and make the isolation of possible products simpler, the MEM protecting group was removed in a small sample of the diprotected dialdehyde to yield the phenolic dialdehyde **3d** . This intermediate was then subjected to the titanium reaction with the hope of isolate a phenolic stilbene directly, but again a very intractable mixture was obtained.

IV.3. CONCLUSIONS. The first, and unavoidable, conclusion from the results described above is that the low-valent titanium induced condensation reaction which is so successful for the simple, non-funcionalized, stilbene cycles prepared in Chapter III, cannot be utilized in a practical manner to synthesize the functionalized stilbenes required in these studies. In view of the results reported by other authors,[69] it seems unlikely that steric hindrance can account for its failure, but very little is known on the compatibility of other functional or protecting groups with this reaction.

Although the titanium reaction could not be successfully utilized to prepare a functionalized stilbene cycle, a great number of other synthetic procedures were either found or adapted for the type of compounds utilized in the course of this research. The HMPA-cosolvent alkylation procedure developed in the preceding chapter for synthesis of ethers

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was found to be very useful for the preparation of other ethers and protected phenols, once the temperature was lowered to account for the high reactivity of the starting halides. Kantlehner's acetalization procedure was modified to produce high yields of phenolic acetals in one step, without prior blocking of the phenol,[134] and a biphasic procedure for the selective acid hydrolysis of acetals with enhanced selectivity was developed.

An experimental method for effecting double hydrogen-lithium exchanges in benzene-hexane solvent was also found. The *bis*(aryllithium) intermediates obtained by this procedure were transformed into *bis*(benzaldehydes) by reaction with DMF in synthetically useful yields (79 and 82 % for **3b** and **3c**, respectively). The reaction of different electrophiles with these and other similar dimetallated intermediates, though not explored in the course of the research described in this dissertation, should provide an attractive method of preparation of unsymmetric *bis*(aryl) ethers.

All the synthetic procedures mentioned above have been utilized, quite successfully, to create a very large pool of synthetic precursors to the desired models. From these intermediates, a wide variety of reactions can lead to the formation of either a stilbene, a diphenyl ethane, or a diphenyl ethyne. The most promising of these alternative synthetic methods are discussed in the appendix to this dissertation.

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IV.4. EXPERIMENTAL SECTION.

General Procedures. Melting points were determined on an Electrothermal apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker WP-200 spectrometer operating at 200 and 50.3 MHz, respectively. 60 MHz ^{1}H NMR spectra were obtained on a Varian A-60A spectrometer using $CDCl_3$. All chemical shifts are expressed as ppm relative to internal TMS, and coupling constants in Hz. IR spectra were obtained on a Perkin Elmer Model 621 grating infrared spectrometer and UV spectra on a Varian Associates Cary 118. Mass spectra were obtained by Mr. Don Patterson on a Hewlett-Packard Model 5985 GC-Mass Spectrometer and are reported as *m/e* (relative intensity). Dioxane was dried by distillation from sodium. THF and ethyl ether were distilled from sodium benzophenone ketyl. Benzene and hexane were succesively washed with conc. sulfuric acid, 10% sodium bicarbonate, distilled water, dried over sodium sulfate, and distilled from calcium hydride under inert atmosphere. Triethylamine (Et_3N) was purified by distillation from NaOH under an argon atmosphere. Methylene chloride was distilled from calcium hydride under nitrogen. Titanium tetrachloride was purified by refluxing over copper scouring pads, followed by distillation. Zinc dust was activated by successively washing with 5% HCl, water, ethanol, ether, and drying *in vacuo*. *N,N* -Dimethylformamide (DMF) was purified by drying over sodium sulfate and distillation from activated

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alumina. *p*-Toluenesulfonyl chloride was recrystallized from petroleum ether. Resorcinol, 3-hydroxy benzaldehyde and 3-hydroxybenzyl alcohol were recrystallized from water. 3-Acetoxyphenol (resorcinol monoacetate) was purified by successive washings with 10% sodium bicarbonate and distilled water, followed by Kugelrohr distillation. Butyllithium was prepared according to standard methods[135] and titrated periodically with 2-butanol in xylene.[136] All the remaining reagents were used as received. All the glassware utilized was oven-dried at 140°C, assembled hot, and cooled under a rapid argon or nitrogen stream.

Dimethylformamide-dimethyl sulfate complex (DD) was prepared according to the procedure of Bredereck[127]. In a 250 mL Erlenmeyer flask with magnetic stirrer, 36.5 g of DMF (0.5 mol) and 63.1 g of Me_2SO_4 (Aldrich, 0.5 mol) were mixed and stirred at 70°C for 2 h. The yellowish oil was cooled to 25°C, washed with 5x20 mL of benzene, then 5x20 mL of Et_2O, and dried *in vacuo*, obtaining 84.2 g (0.42 mol, 84.6% yield) of the complex.

3-(Dimethoxymethyl)phenol (10a) : Under nitrogen atmosphere, 21.2 g of the DD complex (0.10 mol) were mixed with 33.2 mL (1.00 mol) of methanol (Baker) and 10.0 g (0.08 mol) of 3-hydroxybenzaldehyde. The mixture was stirred for 25.5 h at 25°C, cooled to 10°C, and quenched with Et_3N (10.7 g, 0.11 mol). The resulting dark red oil was extracted with 14x50 mL of Et_2O. The organic extracts were successively

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washed with 4x50 mL of 5% $NaHSO_3$, 2x50 mL of H_2O, and 50 mL of brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was extracted with 8x100 mL of boiling hexane. The hexane was removed *in vacuo* obtaining 11.4 g (84.8 %) of a slightly reddish oil. It decomposed on attempted distillation, but it was pure (^1H NMR).

^1H NMR δ 7.22-7.14 (1H5', m), 6.97- 6.79 (3H2'+4'+6', m), 6.33 (1HO-H, br), 5.30 (1H8', s), 3.26 (6H9', s); ^{13}C NMR δ 156.15 (C1', s), 139.03 (C3', s), 129.30 (C5', d, ^1J=161.3), 118.34 (C4', d, ^1J=162.1), 115.67 (C2', d, ^1J=157.7), 113.49 (C6', d, ^1J=158.2), 103.06 (C8', d, ^1J=162.7), 52.64 (C9', q, ^1J=141.2); IR (Neat) 3350, 2940, 2905, 2835, 1598, 1490, 1465, 1363, 1320, 1285, 1205, 1185, 1165, 1112, 1090, 1065, 1005, 980, 930, 885, 835, 795, 715 cm^{-1}; MS *m/e* 170 (M+2, 0.1), 169 (M+1, 1), 168 (M^+, 9), 138 (9) 137 (100), 121 (11.7), 75 (10.6).

3-Methoxy-1-[2-(2-hydroxyethoxy)ethoxy]benzene (16a) : Under a nitrogen atmosphere, 7.9 g (0.19 mol) of NaOH were suspended in 60 mL of HMPA. A solution of 20.0 g of 3-methoxyphenol (Aldrich, 0.16 mol) in 40 mL of dioxane was added, and the mixture refluxed 25 min. A solution of 29.1 g (0.23 mol) of 2-(2-chloroethoxy)ethanol (Aldrich) in 20 mL of dioxane was added over 3.2 h. The mixture was refluxed for 19.5 h, cooled to 25°C, diluted with 200 mL of H_2O and successively extracted with 3x200, 1x100,and 1x50 mL of Et_2O. The combined organic layer was washed with 50 mL of 5%

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KOH, 50 mL of brine, dried over $MgSO_4$, concentrated *in vacuo*, diluted with 200mL of Et_2O and washed with 20mL of 5% KOH. The aqueous layer was neutralized with concentrated HCl and reextracted with 3×20mL of Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to yield 17.4 g of a colorless liquid (it contains *ca* 20.7 % HMPA by NMR), 40.4% yield after correcting for the concentration. An analytical sample was purified by distillation, but the bulk of the material was used directly in the following reaction.

^1H NMR δ 7.13 (1H4", ca. t, Japp=8.3), 6.51-6.46 (3H2"+5"+6", m), 4.07-4.03 (2H4, AA'BB'/2), 3.80-3.76 (2H3, AA'BB'/2), 3.72-3.54 (4H1+2, m), 3.63 (3H8",s); ^{13}C NMR δ 160.62 (C1", s), 159.65 (C3",s), 129.68 (C5",d, ^1J=159.0), 106.52 (C4",d, ^1J=160.8), 106.42 (C6",d, ^1J=160.9), 100.97 (C2",d, ^1J=158.2), 72.50 (C4,t, ^1J=140.4), 69.35 (C3,t, ^1J=142.6), 67.18 (C2,t, ^1J=145.4), 61.39 (C1,t, ^1J=142.8), 55.00 (C8",q, ^1J=143.8); IR (Neat) 3420, 3060, 2930, 2880, 1605, 1498, 1470, 1460, 1365, 1343, 1300, 1278, 1210, 1180, 1168, 1140, 1023, 1010, 983, 905, 850, 780, 758, 705 cm^{-1}; MS *m/e* 214 (M+2, 0.3), 213 (M+1, 2.4), 212 (M^+, 17.1), 181 (1.4), 151 (6.8), 126 (5.1), 125 (70.1), 124 (100), 123 (7.2), 109 (4.7), 108 (6.4), 107 (15.9), 96 (42.7), 95 (39.1), 94 (22.4), 93 (5.4), 92 (21.1), 91 (6.5), 81 (8.7), 80 (6.2), 77 (21.2), 65 (7.7), 64 (10.6), 63 (10), 45 (19.4);

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3-Methoxy-1-[2-(2-hydroxyethoxy)ethoxy]benzene, 4-methylbenzenesulfonate (17a) : A solution of 10.0 g (47.2 mmol) of **16a** in 22 mL of pyridine (Baker, 21.5 g, 272 mmol) was cooled to 0°C in an ice-salt bath. A solution of 13.5 g (70.9 mmol)of *p*-toluenesulfonyl chloride in 100 mL of CH_2Cl_2 was added over 90 min, keeping the temperature at *ca.* 0°C. Stirring was continued at 0°C for 24 h, and 100 mL of an aqueous solution (10% NaOAc, 10% $KHCO_3$) at 0°C were added. The biphasic mixture was stirred vigorously 10 min, phases were separated, the aqueous layer was extracted with 1×100 mL and 1×50 mL of CH_2Cl_2. The combined organic extract was successively washed with 1×50 mL of 5% HCl and 2×50 mL of brine, dried over Na_2SO_4 and concentrated *in vacuo* to yield 18.8 g of a yellow oil (93.2 % product, 6 % *p*-toluene sulfonic acid, 1% HMPA by NMR), quantitative yield after correcting for concentration. The product was satisfactory for use in the following reaction.

^{1}H NMR (60 MHz) δ 7.56 (4H6+7, AB system, $\Delta\nu$=30Hz, J=8), 7.33-7.02 (1H5", m), 6.63-6.40 (3H2"+4"+6", m), 4.28-3.95 (4H1+4, m), 3.83-3.53 (7H2+3+8", m), 2.40 (3H9, s).

1-(Dimethoxymethyl)-3-[2-[2-(3-methoxyphenoxy)ethoxy]-ethoxy]benzene (18a) : A solution of 7.57 g (45 mmol) of **10a** in 50 mL of THF was added in one portion to a suspension of 2.00 g (50 mmol) of NaOH in 50 mL of HMPA. The atmosphere was purged with nitrogen, and the mixture refluxed for 1 h, when total dissolution was achieved. At

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this time, a solution of 15.0 g (41 mmol) of **17a** in 50 mL of THF was added dropwise over 30 min. The resulting reddish suspension was further diluted with 50 mL of THF and refluxed for 4.5 h, cooled down to 25°C and filtered. The filtrate was diluted with 200 mL of H_2O and extracted with 5x140 mL of Et_2O. The combined organic extract was clarified with charcoal, washed with three portions of 5% KOH (100, 70, and 50 mL) and two 200 mL portions of brine, clarified again with charcoal and the solvent removed *in vacuo* to yield (80.9 %) 12.0 g of a dark-red liquid which was pure by NMR.

^{13}C NMR δ 160.54, 159.71, 158.50, 139.48, 129.49, 128.86, 119.01, 114.55, 112.51, 106.40, 106.30, 102.61, 100.91, 69.53, 67.15, 54.78, 52.26.

3-(Dimethoxymethyl)-1-[(2-methoxyethoxy)methoxy]benzene (20a) : Under nitrogen atmosphere, 0.53 g of NaOH (13 mmol) were suspended in 6 mL of HMPA. A solution of 1.00 g (5.95 mmol) of **10a** in 6 mL of THF was added, the mixture was refluxed for 1 h and cooled to 25°C. A solution of 0.65 mL (0.71 g, 5.62 mmol) of MEMCl (Aldrich, methoxyethoxymethyl chloride, 2,5-dioxahexyl chloride) in 6 mL of THF was added dropwise over 1 h. Stirring was continued for 25 h at 25°C, after which the reaction mixture was diluted with 25 mL of 5% KOH and extracted with 3x10 mL of Et_2O. The combined organic extract was washed with 10 mL of NaCl-saturated 5% KOH and concentrated *in vacuo*. The residue was redissolved

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in 25 mL of Et_2O and successively washed with 2X5 mL of 5% KOH and 10 mL of 5% KOH-brine, dried over Na_2SO_4 and concentrated *in vacuo* to yield (95.8 %) 1.41 g of a yellow liquid (ca 1.5% HMPA by NMR).

^1H NMR δ 7.28-6.96 (4H2'+4'+5'+6', m), 5.32 (1H8', s), 5.23 (2H11', s), 3.80-3.75 (2H12', AA'BB'/2), 3.58-3.47 (2H13', AA'BB'/2), 3.31 (3H14', s), 3.28 (6H9', s); ^{13}C NMR δ 156.74 (C1', s), 139.71 (C3', s), 128.86 (C5', d, ^1J=161.0), 119.85 (C4', d, ^1J=162.5), 115.84 (C2', d, ^1J=160.2), 114.38 (C6', d, ^1J=160.5), 102.44 (C8', d, ^1J=161.8), 93.06 (C11', t, ^1J=165.6), 71.26 (C12', t, ^1J=141.7), 67.29 (C13', t, ^1J=143.9), 58.50 (C14', q, ^1J=140.2), 52.19 (C9', q, ^1J=143.6); IR (Neat) 2935, 2895, 2830, 1595, 1497, 1460, 1430, 1390, 1365, 1255, 1203, 1165, 1115, 1090, 1068, 1030, 1000, 950, 885, 820, 790, 715 cm^{-1}; MS *m/e* 258 (M+2, 0.2), 257 (M+1, 1.7), 256 (M^+, 9.5), 225 (16.7), 195 (6.9), 181 (9.2), 149 (12.1), 137 (47.4), 136 (100), 135 (11.1), 121 (16.4), 120 (11.3), 119 (5.9), 109 (5.9), 108 (18.8), 107 (11.5), 105 (7.9), 93 (5), 92 (5.1), 91 (15), 90 (6.7), 89 (61.1), 79 (21.7), 78 (19.2), 77 (19.9), 76 (6.1), 75 (28.3), 65 (13.4), 63 (7.9), 59 (59.8), 51 (5.6), 45 (31.2), 43 (5.6).

1,5-Bis-(3-methoxyphenoxy)-3-oxapentane (27a) : A solution of 15.0 g (121 mmol) of 3-methoxyphenol in 120 mL of THF was added in one portion to a suspension of 4.92 g (123 mmol) of NaOH in 60 mL of HMPA, and the atmosphere was

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purged with nitrogen. The mixture was refluxed for 30 min, and a solution of 25.0 g (121 mmol) of diethylene glycol ditosylate[111] in 100 mL of THF was added dropwise over 15 min. Reflux was continued for 4 h, during which *ca.* 50 mL of THF had to be added because of foaming. The reaction mixture was cooled to 25°C, diluted with 400 mL of 5% KOH and extracted with 1x200 and 2x100 mL of Et_2O. The combined organic extract was successively washed with 2x100 mL of 5% KOH and 100 mL of brine and concentrated *in vacuo* to yield 22.2 g of a dark yellow powder which contained *ca.* 19 % HMPA by NMR. It was redissolved in 250 mL of Et_2O, cooled to -5°C and filtered to yield 10.0 g of yellow powder. The filtrate was washed with 3x40 mL of 5% KOH,dried over Na_2SO_4 and concentrated *in vacuo* to yield an additional 6.9 grams of product. The total purified yield was (88.0 %) 16.9 g. ^1H NMR δ 7.21-7.12 (2H5", m), 6.54-6.48 (6H2"+4"+6", m), 4.16-4.11 (4H4, AA'BB'/2), 3.93-3.89 (4H3, AA'BB'/2), 3.77 (6H8",s); ^{13}C NMR δ 160.81 (C1", s), 160.00 (C3", s), 129.80 (C5", d, ^1J=158.0), 106.73 (C6", d, ^1J=161.6), 106.64 (C4", d,^1J=161.1), 101.20 (C2", d, ^1J=158.4), 69.90 (C4, t, ^1J=144.2), 67.48 (C3, t, ^1J=143.8), 55.22 (C8", q, ^1J=143.6); IR (thin film) 3030, 3020, 2960, 2930, 2900, 2880, 2835, 2760, 1605, 1500, 1470, 1445, 1390, 1370, 1340, 1290, 1275, 1210, 1185, 1165, 1140, 1095, 1070, 1060, 885, 865, 835, 775, 695 cm^{-1}; MS *m/e* 320 (M+2, 0.9), 319 (M+1, 5.8), 318 (M^+, 25.6), 195 (5.8), 194 (30.1), 151 (40.5), 150

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(5.7), 137 (5.3), 125 (13.7), 124 (100), 123 (11.5), 108 (8), 107 (24.9), 96 (9.7), 95 (14.7), 92 (26.1), 91 (9.6), 77 (27.1), 64 (5.1).

3-(2,6-Dioxacyclohexyl)phenol (10b) : A solution of 28.1 g (0.37 mol) of 1,3-propanediol (Aldrich), 23.0 g (0.16 mol) of the DD complex, and 15.0 g (0.123 mol) of 3-hydroxybenzaldehyde in 75 mL of CH_2Cl_2 was stirred at 25°C for 24.5 h, cooled down to 0°C and slowly quenched with 22.5 mL (16.1 g, 0.16 mol) of Et_3N. The resulting black oil was extracted with 5×100 mL of Et_2O. The combined organic extract was washed with 3×50 mL of NaOAc-saturated 5% aq. bisulfite and 50 mL of NaOAc-saturated brine, dried over Na_2SO_4 sulfate and concentrated *in vacuo* to yield (87.2 %) 19.3 g of a white solid, MP 109.5-110.5°C (Lit.[125] MP 109-110°C).

Note : The product decomposed to the corresponding benzaldehyde when a normal aqueous isolation procedure was utilized. Buffering of the aqueous solutions utilized with sodium acetate allowed the prevented this decomposition.

^{1}H NMR δ 7.15 (1H5', ca.t, Japp=7.8), 6.99 (1H4', ca.d, Japp= 7.7), 6.90 (1H2', ca. t, Japp=2.2), 6.69 (1H6', ca. ddd, Japp=8.0, 2.6, 0.8), 6.00 (1HO-H, br), 5.42 (1H8', s), 4.23 (2H9'e, ddd, J_1=11.9, J_2=5.0, J_3=1.2), 3.94 (2H9'a, ddd, J_1=12.5, J_2=11.9, J_3=2.4), 2.19 (1H10'a, dtt, J_1=13.4, J_2=12.5, J_3=5.0), 1.40 (1H10'e, dtt, J_1=13.4, J_2=2.4, J_3=1.2); ^{13}C NMR δ 155.87 (C1', s), 139.74 (C3', s), 129.41

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(C5', d, ^{1}J= 158.9), 117.95 (C6', d, ^{1}J=165.3), 116.03 (C4', d, ^{1}J=157.8), 113.11 (C2', d, ^{1}J=159.6), 101.44 (C8', d, ^{1}J=161.7), 67.26 (C9', t, ^{1}J=144.6), 25.55 (C10', t, ^{1}J=128.6); IR (thin film) 3300, 3045, 2975, 2950, 2925, 2890, 2860, 1610, 1470, 1410, 1395, 1380, 1350, 1325, 1300, 1290, 1250, 1240, 1190, 1170, 1160, 1110, 1030, 995, 960, 930, 875, 815, 720 cm^{-1}; MS *m/e* 182 (M+2, 0.6), 181 (M+1, 5.4), 180 (M^+, 40.3), 179 (73), 163 (16.9), 122 (48.4), 121 (100), 95 (10), 94 (17.3) 93 (22.9), 87 (29.4), 77 (8.9), 65 (19).

3-(2,6-Dioxacyclohexyl)-1-[2-(2-hydroxyethoxy)ethoxy]-benzene (11b) : A solution of 20.0 g (0.111 mol) of **10b** in 100 mL of dioxane was added at once to a suspension of 4.35 g of NaOH (0.111 mol) in 50 mL of HMPA, and the atmosphere was purged with nitrogen. The mixture was then heated to reflux, and a solution of 11.8 g (0.111 mol) of 2-(2-chloroethoxy)ethanol in 100 mL of dioxane was added dropwise over 3.3 h. The reflux was continued for 17.25 h. The mixture was allowed to cool down to 25°C, filtered, and diluted with 200 mL of 5% KOH. The phases were separated and the aqueous layer was extracted with 2x100 + 1x50 mL of Et_2O. The combined organic extract was washed with 2x75 mL of 5% KOH and 75 mL of NaOAc-saturated brine, dried over Na_2SO_4 and concentrated *in vacuo* to obtain 15.0 g (50.4 % yield) of product as a yellow oil.

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^{1}H NMR δ 7.23 (1H5', ca. t, Japp=7.8), 7.05-7.01 (2H2'+4', m), 6.88-6.83 (1H6', m), 5.42 (1H8', s), 4.19 (2H9'e, ca. ddd, Japp=11.3, 4.8, 0.8), 4.10-4.05 (2H1, AA'BB'/2), 3.90 (2H9'a, ca. td, Japp=12.3, 2.0), 3.77-3.72 (2H2, AA'BB'/2), 3.65 (2H3, br), 3.57-3.53 (2H4, m), 3.27 (1HO-H, br), 2.14 (1H10'a, ca. qt, Japp=12.7, 5.1), 1.37 (1H10'e, br dd, Japp=13.5, 1.1); ^{13}C NMR δ 158.29 (C1',s), 139.89 (C3',s), 128.88 (C5', d, ^{1}J=162.1), 118.38 (C6', d, ^{1}J=164.6), 115.13 (C4', d, ^{1}J=167.0), 111.61 (C2', d, ^{1}J=159.8), 100.91 (C8', d, ^{1}J=161.1), 72.29 (C1, t, ^{1}J=153.0), 69.22 (C2, t, ^{1}J=144.0), 67.07 (C9', t, ^{1}J=142.1), 66.91 (C3, t, ^{1}J=140.2), 61.17 (C4, t, ^{1}J=147.3) 25.33 (C10', t, ^{1}J=128.1); IR (Neat) 3430, 3060, 3030, 2950, 2920, 2850, 2723, 1590, 1495, 1450, 1385, 1325, 1285, 1270, 1245, 1190, 1160, 1108, 1075, 1060, 1010, 960, 905, 882, 870, 803, 795, 710 cm^{-1}; MS *m/e* 270 (M+2, 0.8), 269 (M+1, 4.4), 268 (M$^+$, 32.6), 267 (25.7), 209 (17.1), 180 (5.6), 179 (33.4), 165 (3.9), 164 (3.5), 163 (20), 147 (6.0), 135 (7.8), 123 (6.1), 122 (21.6), 121 (46.9), 120 (8.7), 119 (5.4), 107 (9.5), 106 (5), 105 (22.2), 95 (7.6), 94 (17.5), 93 (19.2), 92 (11), 91 (11.6), 89 (10.1), 88 (13.9), 87 (100), 79 (6.8), 78 (5.8), 77 (32.4), 76 (9.2), 75 (5.8), 65 (24.1), 59 (15.7), 51 (5.5), 45 (35.4).

3-(2,6-Dioxacyclohexyl)-1-[2-(2-hydroxyethoxy)ethoxy] benzene, 4-methylbenzene sulfonate (12b) : Under nitrogen atmosphere, a solution of 16.0 g (84 mmol) of *p*-toluenesul-

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fonyl chloride in 100 mL of CH_2Cl_2 was added dropwise to a chilled solution of 15.0 g (56 mmol) of **11b** in 15 mL of pyridine over 1.5 h, keeping 0<T<2°C. The stirring was continued at 0°C for 18.5 h. 100mL 10% of aq NaOAc were added, the phases were separated and the aqueous layer was extracted with 1x100 + 2x50 mL of CH_2Cl_2. The combined organic extract was washed with 75 mL of NaOAc-saturated brine, dried over Na_2SO_4 and concentrated *in vacuo* to yield 25.2 g of a yellow oil. It was redissolved in 200 mL of CH_2Cl_2, washed with 2x75 mL of saturated $NaHCO_3$ and 75 mL of NaOAc-saturated brine, dried over Na_2SO_4, and concentrated *in vacuo* to yield (91.0 %) 21.0 g of a yellow oil. ^1H NMR δ 7.51 (4H6+7, AB system, $\Delta\nu$=96.5 Hz, J=8.2), 7.45-6.97 (4H2'+4'+5'+6', m), 5.45 (1H8', s), 4.29-4.11 (4H9'e+4, m), 4.07-3.87 (4H1+9'a, m), 3.76-3.60 (4H2+3, m), 2.37 (3H9, s), 2.27-2.01 (1H10'a, m), 1.48-1.34 (1H10'e, br d, Japp=13.5).

3-[2-(2-Methoxyethoxy)methoxy]phenol (13b) : Under nitrogen atmosphere, 9.50 g of a 50 % suspension of NaH in oil (Aldrich, 4.75 g, 198 mmol) were washed with 5x20 mL of petroleum ether and suspended in 70 mL of THF. The slurry was cooled to 5°C in an ethylene glycol bath and a solution of 15.0 g of purified 3-acetoxyphenol (98.6 mmol) in 25 mL of THF was added dropwise over 1.5 h, keeping the temperature at or below 10°C. Stirring was continued until hydrogen evolution ceased (20 min) and a solution of 11.3 mL (12.3 g,

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99 mmol) of MEMCl in 30 mL of THF was added dropwise over 2.5 h. The mixture was stirred at 5°C for 19.8 h, when the cooling bath was removed. Stirring was continued at 25°C for 24.25 h. The reaction mixture was slowly quenched with 125 mL of H_2O and stirred at 25°C for 27.25 h to saponify the acetate, washed with 4x20 mL of CH_2Cl_2, acidified to pH 4 with conc. HCl and extracted with 6x25 mL of $CH_2Cl_2$and 6x25 mL of Et_2O. The combined organic extract was successively washed with 4x25 mL of saturated $NaHCO_3$ and 1x50 mL of NaOAc-saturated brine, dried over Na_2SO_4, and concentrated *in vacuo* to yield 17.0 g of a reddish oil (no resorcinol detected by NMR). It was Kugelrohr-distilled to yield (79.5 %) 15.5 g of pure product as a colorless oil, BP 95°C (0.05 mm).

Note: the same reaction was run using technical grade resorcinol monoacetate with a yield of 50.8%. Although the yield was considerably better on using purified material, the low yield of the purification (30.8%) gave an overall yield of 24.5 %. This made for a faster and higher yielding preparation when the technical grade material was used directly.

^1H NMR δ 8.2-7.3 (1HO-H, br s), 7.11-6.93 (1H5", m), 6.56-6.35 (3H2"+4"+6", m), 5.14 (2H8", s), 3.78-3.74 (2H9", AA'BB'/2), 3.55-3.50 (2H10", AA'BB'/2), 3.31 (3H11", s); ^{13}C NMR δ 158.14 (C3",s), 156.90 (C1",s), 130.03 (C5",d, ^1J=159.3), 109.14 (C4", d, ^1J=169.3), 108.27 (C6", d, ^1J=157.8), 103.67 (C2", d, ^1J=163.8), 93.24 (C8", t,

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^1J=166.7), 71.46 (C9", t, ^1J=139.9), 67.27 (C10", t, ^1J=139.9), 58.66 (C11", q, ^1J=142.9); IR (Neat) 3340, 2930, 2860, 1593, 1485, 1460, 1285, 1180, 1150, 1080, 1030, 1000, 950, 853, 778, 695 cm^{-1}; MS *m/e* 200 (M+2, 0.2), 199 (M+1, 1.7), 198 (M^+, 13.4), 123 (13.9), 110 (20.2), 93 (13.6), 90 (4.5), 89 (100), 81 (5.5), 65 (7.5), 59 (75).

1-(2,6-Dioxacyclohexyl)-3-[2-[2-[3-[(2-methoxyethoxy)-methoxy]phenoxy]ethoxy]ethoxy]benzene (18b) : A solution of 2.21 g (11.2 mmol) of **13b** in 10 mL of THF was added in one portion to a suspension of 0.50 g (12.5 mmol) of NaOH in 6 mL of HMPA, and the atmosphere was purged with nitrogen. The resulting mixture was refluxed 20 min and a solution of 4.71 g (11.2 mmol) of **12b** in 15 mL of THF was added dropwise over 10 min. The reaction mixture was refluxed 3.5 h and stirred at 25°C for 16.5 h. After this period, it was filtered and the filtrate was diluted with 75 mL of Et_2O. The phases were separated and the aqueous layer was extracted with 4x50 mL of Et_2O. The combined organic extract was successively washed with 4x35 mL of 5% KOH and 1x50 mL of NaOAc-saturated brine, dried over Na_2SO_4 and the solvent removed *in vacuo* to yield (89.0 %) 4.45 g of product as a yellowish oil. ^1H NMR δ 7.28 (4H2'+4'+5'+5", m), 6.91-6.85 (1H6', m), 6.67-6.54 (3H2"+4"+6", m), 5.44 (1H8', s), 5.22 (2H8', s), 4.27-3.86 (12H1+2+3+4+9, m), 3.82-3.77 (2H9", AA'BB'/2), 3.55-3.51 (2H10", AA'BB'/2), 3.35 (3H11", s), 2.28-2.09 (1H10'a, m), 1.42-1.37 (1H10'e, m); ^{13}C NMR δ 159.67 (C1',

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s), 158.48 (C3", s), 158.16 (C1", s), 140.36 (C3', s), 129.69 (C5'+5", d, ^1J=158.0), 118.62 (C4', d, ^1J=161.0), 115.47 (C2', d, ^1J=159.4), 112.26 (C6', d, ^1J=159.8), 108.93 (C6", d, ^1J=159.2), 108.40 (C4", d, ^1J=160.7), 103.75 (C2", d, ^1J=159.4), 101.28 (C8', d, ^1J=159.8), 93.65 (C8", t, ^1J=165.4), 69.72 (C4, t, ^1J=142.4), 69.66 (C1, t, ^1J=141.9), 68.84 (C9", t, ^1J=136.8), 67.47 (C10", t, ^1J=144.5), 67.33 (C2+3, t, ^1J=143.9), 67.07 (C9', t, ^1J=141.2), 58.70 (C11', q, ^1J=141.1), 25.75 (C10', t, ^1J=128.1); IR (Neat) 3042, 2900, 2795, 1605, 1593, 1495, 1455, 1385, 1286, 1270, 1245, 1192, 1143, 1115, 1025, 962, 870, 785, 705 cm^{-1}; MS *m/e* 149 (10.4), 147 (7.9), 137 (6.9), 121 (19), 120 (6.2), 119 (4.2), 115 (11.3), 110 (4.5), 107 (5.7), 105 (9.7), 103 (4.1), 93 (11), 92 (15.8), 91 (8.5), 89 (91.5), 87 (34.3), 79 (5.3), 77 (14.9), 65 (8.1), 64 (6.2), 60 (3.9), 59 (100).

2-(2,6-Dioxacyclohexyl)-6-[2-[2-[3-[(2-methoxyethoxy)-methoxy]-2-carboxyaldehydephenoxy]ethoxy]ethoxy]benzaldehyde (3b) : Under nitrogen atmosphere a solution of 5.0 g (11.2 mmol) of **18b** in 30 mL of dry benzene was added dropwise over a solution of 19.3 mL of 1.77 M BuLi in hexane in 70 additional mL of dry hexane over 43 min, while keeping T<5°C in an ice-salt bath. The resulting suspension was kept at 0°C 30 min, and 10.6 mL (8.14 g, 112 mmol) of DMF were added dropwise over 10 min. The cooling bath was removed and the reaction mixture stirred at 25°C for 6.7 h. The reaction was then quenched with 30 mL of 5% KOH. The phases were sepa-

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rated and the aqueous layer was extracted with 6×50 mL portions of Et_2O. The combined organic extract was successively washed with 3×30 mL of 5% KOH and 1×50 mL of NaOAc-saturated brine, dried over Na_2SO_4 and concentrated *in vacuo* to yield (79.0 %) 4.44 g of product as a brown oil.
^1H NMR δ 10.60 (1H7', s), 10.51 (1H7", s), 7.54-7.45 (2H4'+5', AA'B2/3), 7.38 (1H5", ca t, Japp=8.5), 7.07-6.91 (1H6', AA'B/3), 6.82 (1H4", ca d, Japp=8.5), 6.61 (1H6", ca dd, Japp=8.3, 2.7), 6.25 (1H8', s), 5.24 (2H8", s), 4.27-3.81 (12H1+2+3+4+9', m), 3.79-3.65 (2H9", AA'BB'/2), 3.56-3.49 (2H10", AA'BB'/2), 3.34 (3H11", s), 2.24-2.15 (1H10'a, m), 1.45-1.38 (1H10'e, m).

2-[2-(1-Methoxy-1-methylethoxy)ethoxy]ethyl chloride (14) : A few crystals of trichloroacetic acid (Fischer) were added to a suspension of 17.0 mL (20.0 g, 160 mmol) of 2-(2-chloroethoxy)ethanol in 20 mL of Et_2O, and the atmosphere was purged with nitrogen. 2-Methoxypropene (Aldrich) (18.8 g, 261 mmol) was added at such a rate to keep the temperature between 37 and 42°C (t=25 min). The mixture was stirred at 25°C for 1 h and then poured over 30 mL of 10% NaOH with vigorous stirring. The phases were separated and the aqueous layer extracted with 3×30 mL of Et_2O. The combined organic extract was washed with 3×20 mL of 5% KOH +30 mL of NaOAc-saturated brine, dried over Na_2SO_4 and concentrated *in vacuo* to yield (90.0 %) 28.3 g of a colorless liquid, BP 73-75°C (0.035 mm).

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Note : This material is highly sensitive towards heating and acid.

^{1}H NMR δ 3.79-3.72 (2H2, m), 3.68-3.63 (4H3+4, m), 3.60-3.53 (2H1, m), 3.20 (3H7, s), 1.34 (6H6, s); ^{13}C NMR δ 99.82 (C5, s), 71.20 (C3, t, ^{1}J=144.2), 70.64 (C2, t, ^{1}J=141.5), 59.99 (C1, t, ^{1}J=141.4), 48.22 (C7,q, ^{1}J=141.7), 42.50 (C4, t, ^{1}J=150.7), 24.22 (C6, q, ^{1}J=125.3); IR (Neat) 3030, 2900, 2915, 1470, 1445, 1392, 1382, 1313, 1272, 1230, 1200, 1170, 1145, 1105, 1060, 975, 920, 845, 765, 685 cm^{-1}; MS *m/e* 167 (15.7), 165 (47.9), 137 (10.6), 119 (7.2), 109 (13.2), 107 (33.8), 95 (5.7), 93 (9.8), 73 (100), 65 (12.1), 63 (31), 45 (11.5), 43 (13.8), 28 (10.8).

1-{2-[2-(1-Methoxy-1-methylethoxy)ethoxy]ethoxy}-3-[(2-methoxyethoxy)methoxy]benzene (15b) : A solution of 9.90 g (50 mmol) of **13b** in 40 mL of dioxane was added in one portion to a suspension of 2.50 g of NaOH (63 mmol) in 20 mL of HMPA. The atmosphere was purged with argon, and the mixture refluxed for 25 min. A solution of 9.85 g (50 mmol) of **14** in 40 mL of dioxane was added dropwise over 70 min. Reflux was continued for 21.5 h. The was allowed to reach 25°C and filtered. The filtrate was diluted with 100 mL of Et_2O and 100 mL of 5% KOH. Phases were separated and the aqueous layer extracted with 2x100 and 2x50 mL of Et_2O. The combined organic extract was successively washed with 2x50 mL of 5% KOH and 50 mL of NaOAc-saturated brine, dried over Na_2SO_4 and concentrated *in vacuo* to yield (95.0 %) 17.0 g of product as a yellow liquid, BP 185-189°C (0.35 mm).

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^{1}H NMR δ 7.18-7.08 (1H5", m), 6.64-6.46 (3H2"+4"+6", m), 5.21 (2H8", s), 4.10-3.36 (12H1+2+3+4+9"+10", m), 3.33 (3H11", s), 3.19 (3H7, s), 1.33 (6H6, s); ^{13}C NMR δ 159.94 (C3", s), 157.95 (C1", s), 129.22 (C5", d, ^{1}J=158.1), 109.04 (C5, s), 108.05 (C4", d, ^{1}J=162.3), 107.44 (C6", d, ^{1}J=160.9), 102.66 (C2", d, ^{1}J=159.2), 92.82 (C8", t, ^{1}J≠165.6), 70.95 (C9", d, ^{1}J=141.7), 70.28 (C4, t, ^{1}J=141.3), 69.01 (C3, t, ^{1}J=141.6), 67.08 (C10", t, ^{1}J=143.7), 66.91 (C2, t, ^{1}J=143.7), 59.56 (C1, t, ^{1}J=151.6), 58.16 (C11", q, ^{1}J=140.1), 47.67 (C7, q, ^{1}J=141.7), 23.79 (C6, q, ^{1}J= 126.3); IR (Neat) 3060, 2935, 2880, 2840, 1603, 1590, 1495, 1460, 1378, 1290, 1268, 1190, 1163, 1138, 1090, 1020, 1003, 857, 780, 700 cm^{-1}; MS *m/e* 358 (M^+, 0.4), 238 (6.1), 210 (5.1), 180 (6.2), 149 (5.7), 137 (14.3), 136 (26.2), 135 (4.6), 110 (12.8), 92 (18), 89 (79.4), 76 (5.3), 74 (4.7), 73 (100), 64 (4.7), 59 (63.3).

3-[(2-Methoxyethoxy)methoxy]-1-[2-(2-hydroxyethoxy)-ethoxy]benzene (16b) : In a 500 mL Erlenmeyer flask 15.0 g (41.9 mmol) of **15b** were dissolved in 250 mL of $CHCl_3$. 100 mL of H_2O, 30 mL of MeOH, and 15 mL of concentrated HCl were added, and the biphasic mixture was stirred for 22 h at 25°C. The phases were separated, the aqueous phase was extracted with 3x50 mL of $CHCl_3$, alkalinized to pH=9 with 5% KOH and extracted with 2x30 mL of $CHCl_3$ and 1x40 mL of Et_2O. The combined organic extract was washed with 30 mL of NaOAc-saturated brine, dried over Na_2SO_4 and concentrated *in*

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vacuo to yield 11.4 g of a colorless liquid. By NMR it contains approximately 8 % HMPA, 10.4 g product, 86.7 % yield. A sample was purified by distillation, but the bulk of the compound was used directly in the next reaction. BP 171-173°C (0.01 mm).

^{1}H NMR δ 7.16 (1H5", ca.t, Japp=8.4), 6.69-6.54 (3H2"+4"+6", m), 5.24 (2H8", S), 4.18-4.09 (2H4, AA'BB'/2), 3.87-3.62 (8H1+2+3+9", m), 3.57-3.51 (2H10", AA'BB'/2), 3.37 (3H11", s), 2.57 (1HO-H, br); ^{13}C NMR δ 159.32 (C3", s), 157.96 (C1", s), 129.34 (C5", d, ^{1}J=158.8), 108.28 (C4", d, ^{1}J=162.1), 107.58 (C6", d, ^{1}J=160.9), 102.79 (C2", d, ^{1}J=159.3), 92.92 (C8", t, ^{1}J=166.0), 72.23 (C9", t, ^{1}J=191.1), 71.03 (C4, t, ^{1}J=141.4), 68.99 (C2, t, ^{1}J=142.3), 67.07 (C1, t, ^{1}J=139.7), 66.93 (C10", t, ^{1}J=144.1), 60.98 (C3, t, ^{1}J=142.2), 58.26 (C11", q, ^{1}J=140.7); IR (Neat) 3430, 3060, 2960, 1595, 1490, 1457, 1420, 1370, 1293, 1270, 1160, 1115, 1010, 945, 897, 853, 780, 747, 698 cm^{-1}; MS *m/e* 288 (M+2, 0.1), 287 (M+1, 0.6), 286 (M$^+$, 3.8), 210 (11.1), 136 (3.9), 111 (5.4), 110 (10.4), 101 (6.7), 93 (5.5), 92 (6.9), 90 (4.1), 89 (100), 76 (4.5), 64 (4.9).

3-[(2-Methoxyethoxy)methoxy]-1-[2-(2-hydroxyethoxy)-ethoxy]benzene, 4-methylbenzenesulfonate (17b) : under nitrogen atmosphere 7.5 g (26 mmol) of **16b** were dissolved in 12 mL of pyridine (5.4 g, 68 mmol) and 10 mL of CH_2Cl_2, and cooled down to 0°C. A solution of 6.5 g of *p*-toluenesulfonylchloride (34 mmol) in 15 mL of CH_2Cl_2

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was added dropwise over 30 min, keeping 0<T<4°C. The reaction mixture was kept at 0°C for 24 h and poured over 100 g of ice with vigorous stirring. Once the ice melted, phases were separated and the aqueous layer extracted with 3x50 mL of CH_2Cl_2. The combined organic extract was successively washed with 3x30 mL of 5% HCl, 30 mL of 10% $NaHCO_3$, dried over Na_2SO_4 and concentrated *in vacuo* to yield (81.3 %) 9.4 g of a slightly yellowish oil.

^{1}H NMR δ 7.51 (4H6+7, AB system, $\Delta\nu$=98.3 Hz, J=8.2), 7.13 (1H5", ca.t, Japp=8.1), 6.67-6.48 (3H2"+4"+6", m), 5.21 (2H8", s), 4.17-4.13 (2H1, AA'BB'/2), 3.98-3.94 (2H4, AA'BB'/2), 3.80-3.76 (2H9", AA'BB'/2), 3.72- 3.63 (4H2+3, m), 3.54-3.49 (2H10", AA'BB'/2), 3.32 (3H11", s), 2.35 (3H9, s); ^{13}C NMR δ 159.34 (C3", s), 158.01 (C1", s), 144.31 (C5, s), 132.57 (C8, s), 129.35 (C7, d, ^{1}J=172.0), 129.57 (C5", d, ^{1}J=158.1), 127.35 (C6, d, ^{1}J=166.1), 108.34 (C4", d, ^{1}J=161.3), 107.57 (C6", d, ^{1}J=160.8), 102.90 (C2", d, ^{1}J=159.3), 93.01 (C8', t, ^{1}J=165.8), 71.07 (C1, t, ^{1}J=142.7), 69.18 (C9", t, ^{1}J=142.3), 68.88 (C2, t, ^{1}J=149.0), 68.25 (C3, t, ^{1}J=142.6), 67.17 (C10", t, ^{1}J=145.7), 66.90 (C4, t, ^{1}J=150.4), 58.29 (C11", q, ^{1}J=142.0), 20.96 (C9, q, ^{1}J=127.4); MS *m/e* 441 (M+1, 0.3), 440 (M^+, 1.6), 199 (15.8), 155 (12.8), 137 (3.3), 110 (8.2), 92 (9.4), 91 (35.7), 90 (5.6), 89 (100), 65 (4.2), 59 (49.6).

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6-{2-[2-(1-Methoxy-1-methylethoxy)ethoxy]ethoxy}-2-[(2-methoxyethoxy)methoxy]benzaldehyde (24b) : Under an argon atmosphere 20.0 g (55.9 mmol) of **15b** were dissolved in 120 mL of Et_2O and cooled down to -35°C in an ethylene glycol-water-dry ice bath. 60 mL of a 1.54M solution of BuLi in hexane (84.7 mmol) were slowly added (20 min) keeping the temperature below -25°C. Stirring was continued at -30°C for 3 h. At this time, 16 mL (12.2 g, 168 mmol) of DMF were added slowly, keeping the temperature below -5°C. The cooling bath was then removed and the reaction mixture stirred at 25°C for 1 h. The reaction was quenched with 100 mL of 5% KOH, phases were separated and the aqueous layer was extracted with 6x50 mL of Et_2O. The combined organic extract was successively washed with 2x50 mL of 5% KOH and 1x75 mL of NaOAc-saturated brine, dried over Na_2SO_4 and concentrated *in vacuo* to yield (95.1 %) 20.5 g of a yellow liquid, BP 241-248°C (0.25 mm).

^1H NMR δ 10.52 (1H7", s), 7.44-7.34 (1H5", m), 6.90-6.80 (1H4", m), 6.66-6.51 (1H6", m), 5.33 (2H8", s), 4.23-3.51 (12H1+2+3+4+9"+10", m), 3.33 (3H11", m), 3.18 (3H7, m), 1.33 (6H6, s); IR (Neat) 3070, 2940, 2890, 2840, 1685, 1600, 1590, 1478, 1415, 1378, 1260, 1200, 1080, 1040, 965, 885, 840, 798; cm^{-1}; MS *m/e* 293 (5), 278 (5.1), 277 (19), 239 (5.5), 238 (16.3), 225 (5.5), 189 (5.3), 181 (5), 165 (6), 164 (35), 151 (14), 138 (5), 137 (17.2), 136 (14.6), 107 (5.3), 103 (7), 90 (5), 89 (84.9), 59 (100), 45 (12.4).

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2-[2-(2-Hydroxyethoxy)ethoxy]-6-[(2-methoxyethoxy)-methoxy]benzaldehyde (25b) : In a 250 mL Erlenmeyer flask 4.22 g (10.9 mmol) of **24b** were dissolved in 100 mL of $CHCl_3$. 40 mL of H_2O, 10 mL of MeOH, and 3 mL of conc. HCl were added and the biphasic mixture was vigorously stirred at 25°C for 19 h. Phases were separated and the aqueous layer was extracted with 2x50 mL of $CHCl_3$. The aqueous layer was taken to pH=8 with 10% NaOH and extracted with 2x25 mL of $CHCl_3$. The combined organic extract was washed with 2x15 mL of saturated $NaHCO_3$, dried over Na_2SO_4 and concentrated *in vacuo* to yield (99.8 %) 3.43 g of a yellow oil. ^1H NMR δ 10.50 (1H7", s), 7.40 (1H5", t, J=8.4), 6.82 (1H4", d, J=8.4), 6.61 (1H6", d, J=8.4), 5.34 (2H8", s), 4.20-4.16 (2H4, m), 3.90-3.83 (2H3, m), 3.83-3.81 (2H9", m), 3.74-3.72 (2H2, m), 3.68-3.64 (2H1, m), 3.56-3.52 (2H10", m), 3.35 (3H11", s); ^{13}C NMR δ 189.16 (C7", d, ^1J=181.9), 160.83 (C3", s), 159.58 (C1", s), 135.58 (C5", d, ^1J=159.6), 107.59 (C4", dd, ^1J=164.1, ^3J=7.3), 107.02 (C2", s), 105.90 (C6", dd, ^1J=161.6, ^3J=7.5), 93.61 (C8", t, ^1J=167.4), 72.51 (C4, t, ^1J=141.3), 71.33 (C9", t, ^1J=141.5), 68.99 (C3, t, ^1J=142.1), 64.43 (C2, t, ^1J=135.5), 68.00 (C10", t, ^1J= 144.3), 61.52 (C1, t, ^1J=141.8), 58.77 (C11", q, ^1J=140.6); IR (Neat) 3450, 2930, 2870, 1690, 1600, 1470, 1415, 1375, 1255, 1200, 1080, 1040, 925, 795, 742 cm^{-1}; MS *m/e* 315 (M+1, 0.3), 314 (M^+, 1.6), 239 (4.6), 238 (13.3), 225 (4.8), 181 (4.5), 180 (6.9), 165 (5.7), 164 (28), 152 (13.0), 151

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(12.1), 138 (5.1), 137 (18), 136 (15), 111 (5.5), 110 (6), 92 (5.7), 90 (5.1), 89 (95.8), 87 (6), 73 (5.7), 65 (4.3), 59 (100).

2-[2-(2-Hydroxyethoxy)ethoxy]-6-[(2-methoxyethoxy)-methoxy]benzaldehyde, 4-methylbenzene sulfonate (26b) : Under nitrogen atmosphere, 3.30 g (10.5 mmol) of **25b** were dissolved in 5 mL of pyridine and 5 mL of CH_2Cl_2 and cooled to -7°C in an ice-salt bath. A solution of 2.65 g (13.9 mmol) of *p*-toluenesulfonyl chloride in 17 mL of CH_2Cl_2 was added over 35 min, keeping T<-5°C. The mixture was stirred in the bath an additional 20 min, the flask was sealed, and kept at -10°C for 21.8 h. The heterogeneous mixture was poured over 70 g ice with vigorous stirring. The ice was allowed to melt and the phases were separated. The aqueous layer was extracted with 3x30 mL of CH_2Cl_2. The combined organic extract was washed with 3x15 mL of 5% HCl and 2x20 mL of saturated $NaHCO_3$, dried over Na_2SO_4 and the solvent was removed *in vacuo*. An NMR spectrum indicated that conversion was incomplete, probably due to exceedingly low temperature. The treatment was repeated, this time keeping the reaction mixture at *ca.* 0°C. After the solvent had been removed (86.9 %) 4.27 g of product (pure by NMR) as a yellow oil were obtained.

^{1}H NMR δ 10.46 (1H7'', s), 7.54 (4H6+7, AB system, $\Delta\nu$=91.8 Hz, J=8.2), 7.40 (1H5'', t, J=8.4), 6.83 (1H4'', d, J=8.4), 6.59 (1H6'', d, J=8.4), 5.34 (2H8'', s), 4.19-4.08 (4H1+4, m),

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3.867-3.70 (6H2+3+9'', m), 3.56-3.52 (2H10'', m), 3.35 (3H11'', s), 2.41 (3H9, s).

3-[(2-Methoxyethoxy)methoxy]benzaldehyde (19a) : Under nitrogen atmosphere, 4.50 g of dry K_2CO_3 (32.8 mmol) were added to a solution of 2.00 g (16.4 mmol) of 3-hydroxybenzaldehyde in 15 mL of DMF. The heterogeneous mixture was heated to 60°C with vigorous stirring. Once this temperature was reached, a solution of 2.45 g (19.6 mmol) of MEMCl in 5 mL of DMF was added dropwise over 10 min. No starting material could be detected by TLC (Silica gel, 5% MeOH in CH_2Cl_2 v/v) after the addition was finished. The reaction mixture was then cooled to 25°C, diluted with 150 mL of distilled water, and extracted with 4x30 mL portions of Et_2O. The combined organic extract was washed with 4x15 mL of 5% KOH and 30 mL of NaOAc-saturated brine, dried over Na_2SO_4 and the solvent removed *in vacuo* to yield (54.2 %) 1.87 g of pure product as a yellow liquid.
^{1}H NMR δ 9.92 (1H8', s), 7.55-7.50 (1H4', m), 7.48-7.46 (1H2', m), 7.41 (1H5', ca t, Japp=7.6), 7.33-7.27 (1H6', m), 5.30 (2H11', s), 3.84-3.79 (2H12', AA'BB'/2), 3.55-3.50 (2H13', AA'BB'/2), 3.31 (3H14', s); ^{13}C NMR δ 191.00 (C8', d, ^{1}J=175.6), 157.08 (C1' , s), 137.17 (C3' , s), 129.33 (C5' , d, ^{1}J=163.2), 122.76 (C4' , d, ^{1}J=163.2), 121.90 (C2' , d, ^{1}J=162.1), 115.34 (C6' , d, ^{1}J=162.4), 92.65 (C11', t, ^{1}J=166.7), 70.76 (C12', t, ^{1}J=142.4), 67.12 (C13', t, ^{1}J=141.7), 57.89 (C14', q, ^{1}J=140.8); IR (Neat) 3060, 2900,

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2815, 2730, 1700, 1595, 1490, 1460, 1400, 1330, 1255, 1160, 1110, 1030, 1000, 940, 910, 865, 810, 790, 755, 700 cm^{-1}; MS *m/e* 211 (M+1, 0.2), 210 (M^+,1.2), 135 (5.5), 121 (4.8), 105 (5), 90 (4.2), 89 (100), 79 (4.4), 77 (8.9), 59 (56.8).

3-[(2-Methoxyethoxy)methoxy]-1-(2,6-dioxacyclohexyl)-benzene (20b) : Under nitrogen atmosphere, 4.44 g (111 mmol) of NaOH were suspended in 30mL of HMPA. A solution of 10.0 g of **10b** (55.6 mmol) in 60 mL of THF was added in one portion. The mixture was refluxed for 1 h and cooled to 25°C. Then, a solution of 10.0 g (55.6 mmol) of MEMCl in 60 mL of THF was added dropwise over 20 min. The resulting mixture was stirred 16 h at 25°C, filtered, diluted with 150 mL of 5% KOH and extracted with 10×25 mL of Et_2O. The combined organic extract was successively washed with 3×25 mL of 5% KOH and 1×50 mL of NaOAc-saturated brine, dried over Na_2SO_4 and concentrated *in vacuo* to yield (95.5 %) 14.2 g of a dark red oil.

^1H NMR δ 7.24 (1H5', ca t, Japp=7.8), 7.17 (1H2', ca t, Japp=1.4), 7.09 (1H4', ca d, Japp=7.6), 6.99 (1H6', ca ddd, Japp=8.0, 1.4, 0.9), 5.41 (1H8', s), 5.22 (2H11", s), 4.18 (2H9'e, dd, J=11.1, 5.0), 3.88 (2H9'a, td, J=12.1, 1.8), 3.78-3.73 (2H12', AA'BB'/2), 3.50-3.46 (2H13', AA'BB'/2), 3.30 (3H14', s), 2.13 (1H10'a, qt, J=12.7, 5.3), 1.34 (1H10'e, dd, J=13.4, 0.7); ^{13}C NMR δ 156.98 (C1', s), 140.11 (C3', s), 129.04 (C5', d, ^1J=161.0), 119.33 (C6', d, ^1J=163.2), 116.40 (C4'd, ^1J=162.4), 113.78 (C2', d,

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^1J=160.4), 101.05 (C8', d, ^1J=161.0), 93.18 (C11', t, ^1J=166.3), 71.38 (C12', t, ^1J=142.1) 67.38 (C13', t, ^1J=146.0), 67.08 (C9', t, ^1J=144.2), 58.66 (C14', q, ^1J=140.2), 25.52 (C10', t, ^1J=128.5); IR (Neat) 3040, 2940,2880, 1593, 1491, 1455, 1385, 1283, 1246, 1155, 1105, 1030, 1000, 870, 803, 710 cm^{-1}; MS *m/e* 270 (M+2, 0.1), 269 (M+1, 0.9), 268 (M^+, 5.4), 179 (5.5), 121 (5.6), 89 (100),87 (17.1), 77 (5.9), 65 (4.4), 59 (79.9).

3-(1-Methoxy-1-methylethoxy)-1-(2,6-dioxacyclohexyl)-benzene (20b') : A few crystals of trichloroacetic acid were added to a solution of 5.00 g of **10b** (27.8 mmol) in 25 mL of Et_2O. Then, with vigorous stirring, 6.00 g (83.3 mmol) of 2-methoxypropene were added dropwise. After 10 min, an additional 6 g of 2-methoxypropene were added and mixture stirred 10 min. The reaction mixture was then poured over 30 mL of 25% KOH. The phases were separated and the aqueous layer was extracted with 3X20 mL of Et_2O. The combined organic extract was dried over Na_2SO_4 and concentrated in vacuo to yield (92.9 %) 6.75 g of a slightly yellowish liquid. This compound was pure except for *ca.* 5 % (by NMR) of the polymerization byproduct of 2-methoxypropene, but its extremely sensitivity to both heat and acid prevented its purification by PTLC on silica gel or distillation.
^1H NMR (60 MHz) δ 7.25-7.07 (4H2'+4'+5'+6', m), 5.42 (1H8', s), 4.38-3.63 (4H9', m), 3.37 (3H13', s), 2.33-1.78 (1H10'a, m), 1.43 (6H12', s), 1.40-1.17 (1H10'e, m).

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6-[(2-Methoxyethoxy)methoxy]-2-(2,6-dioxacyclohexyl)-benzaldehyde (22b) : Under nitrogen atmosphere, 4.00 g of **20b** (15 mmol) were dissolved in 20 mL of dry benzene and 60 mL of dry hexane . The solution was cooled to -10°C in an ice-salt bath. Then, 11.5 mL of a 1.6M solution of BuLi in hexane (18 mmol) were added over 15 min keeping the temperature below 0°C, and the mixture was allowed to stay, without stirring, at 0>T>-5°C for 45 min. After this period 14.2 mL (10.9 g, 150 mmol) of DMF were added in one portion, and the resulting mixture stirred at 0°C for 20 min and at 25°C for another 20 min. 50 mL of 5% KOH were added, the phases were separated and the aqueous layer extracted with 3x50 mL of Et_2O. The combined organic extract was washed with 50 mL of 5% KOH and 50 mL of NaOAc-saturated-brine, dried over Na_2SO_4, and concentrated *in vacuo* to yield 4.40 g of a yellowish oil (it contained approximately 4 % starting material and 3 % 1,2,4-isomer by NMR), 92.5 % yield.
^1H NMR δ 10.58 (1H7', s), 7.47 (1H4'+5', AA'B2/3), 7.23 (1H6', AA'B/3), 6.20 (1H8', s), 5.31 (2H11', s), 4.17 (2H9'e, dd, J=10.8, 5.3), 3.99 (2H9'a, td, J=10.8, J=2.2), 3.78 (2H12', AA'BB'/2), 3.50 (2H13', AA'BB'/2), 3.30 (3H14', s), 2.15 (1H10'e, ddd, J=13.4, 10.8, 5.3), 1.39 (1H10'a, dd, J=13.4, 2.2).

3-[(2-Methoxyethoxy)methoxy]benzenemethanol (19c) : A solution of 20.0 g (0.161 mol) of recrystallized 3-hydroxybenzyl alcohol in 250 mL of THF was added in one

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portion to a suspension of 7.75 g (0.194 mol) of NaOH in 40 mL of HMPA, and the atmosphere was purged with nitrogen. The mixture was refluxed 30 min and cooled down to 25°C. A solution of 17.5 mL (19.1 g, 0.153 mol) of MEMCl in 100 mL of THF was added dropwise over 80 min, and the mixture stirred at 25°C for 16.7 h. The resulting suspension was filtered, diluted with 50 mL of 5% KOH and the phases separated. The aqueous layer was extracted with 5x100 mL portions of Et_2O. The combined organic extract was successively washed with 3x25 mL of 5 % KOH and 1x30 mL of NaOAc-saturated brine, dried over $Na2SO_4$ and concentrated *in vacuo* to yield 34.3 g of a yellowish liquid that contains *ca.* 19 % (w/w) HMPA by NMR (81 % conc, 27.7 g, 85.3 % yield). A sample was purified by distillation, BP 100-103°C (0.02 mm), but the bulk of the material was used directly in the following reaction.

^{1}H NMR δ 7.19 (1H5', ca.t), 6.94 (3H2'+4'+6', m), 5.17 (2H10', s), 4.51 (2H8', br.s), 4.03 (1HO-H , br), 3.73 (2H11', AA'BB'/2), 3.46 (2H12', AA'BB'/2) , 3.27 (3H13', s); ^{13}C NMR δ 156.68 (C1', s), 142.55 (C3', s), 128.76 (C5', d, ^{1}J=160.6), 119.65 (C4', d, ^{1}J=160.8), 114.41 (C2', d, ^{1}J=160.1), 114.02 (C6', d, ^{1}J=154.3), 92.72 (C10', t, ^{1}J=166.2), 70.93 (C8', d , ^{1}J=140.8), 66.89 (C11', t, ^{1}J=142.6), 63.62 (C12', t, ^{1}J=142.3), 58.04 (C13', q, ^{1}J=141.1); IR (Neat) 3480, 3060,2950, 2880, 1590, 1490, 1455, 1252, 1150, 1090, 1020, 995, 855, 795, 700 cm^{-1}; MS

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m/e 213 (M+1, 0.5), 212 (M^+, 4.6), 107 (7.6), 95 (4.8), 90 (5.9), 89 (100), 77 (11.1), 59 (47.7).

3-[(2-Methoxyethoxy)methoxy]-1-methoxymethylbenzene (20c) : Under a nitrogen atmosphere, 5.8 g of a 50% suspension of NaH in oil (2.9 g, 120 mmol) were washed with 3×20 mL portions of hexane and suspended in 60 mL of dry THF. A solution of 21.2 g (100 mmol) of **19c** in 100 mL of dry THF was added dropwise over 15 min. The mixture was stirred at 25°C until the evolution of hydrogen gas ceased (30 min) and then a solution of 7.10 mL (16.2 g, 114 mmol) of MeI (Mallinckrodt) in 60 mL of THF was added over 15 min. The yellowish reaction mixture was stirred at 25°C for 85 min and quenched very carefully with 100 mL of 5 % KOH. This mixture was extracted with 4×75 mL of Et2O, and the combined organic extract was washed with 2×50 mL of 5% KOH and 1×100 mL of NaOAc-saturated brine, dried over Na_2SO_4 and concentrated *in vacuo* to yield (97.9 %) 22.1 g of an almost colorless liquid, BP 100°C (0.05 mm).

^{1}H NMR δ 7.27-7.19 (1H5', ca.ddd), 7.04-7.01 (1H2', m), 6.99-6.96 (1H4', m), 6.95-6.92 (1H6', m), 5.24 (2H10', s), 4.40 (2H8', s), 3.82-3.77 (2H11', AA'BB'/2), 3.55-3.50 (2H12', AA'BB'/2), 3.36 (3H9', s), 3.34 (3H13', s); ^{13}C NMR δ 156.96 (C1', s), 139.45 (C3', s), 128.81 (C5', d, ^{1}J=160.5), 120.46 (C4', d, ^{1}J=160.6), 114.95 (C2', d, ^{1}J=154.9) 114.89 (C6', d, ^{1}J=159.7), 92.89 (C10', t, ^{1}J=165.6), 73.77 (C8', t, ^{1}J=145.8), 71.06 (C11', t,

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^1J=140.5), 67.11 (C12', t, ^1J=143.4), 58.22 (C9', q, ^1J=140.7), 57.80 (C13', q, ^1J=140.8); IR (Neat) 3020, 2940, 2900, 2840, 1595, 1490, 1455, 1385, 1370, 1253, 1205, 1160, 1100, 1020, 995, 930, 860, 795 cm^{-1}; MS *m/e* 227 (M+1, 0.3), 226 (M^+, 2.1), 121 (6.8), 108 (5.1), 91 (7), 90 (6.5), 89 (100), 77 (8.2), 59 (54.7).

3-(Methoxymethoxy)benzenemethanol (19c') : A solution of 25.0 g (0.201 mol) of recrystallized 3-hydroxybenzyl alcohol in 200 mL of THF was added in one portion to a suspension of 18.1 g (0.452 mol) NaOH in 40 mL of HMPA, and the atmosphere was purged with nitrogen. The mixture was refluxed for 1 h, and then cooled to 25°C. At this point, a solution of 16.9 mL (17.8 g, 0.220 mol) of MOMCl (Aldrich, Methoxymethyl chloride, 2-oxapropyl chloride) in 100 mL of THF was added dropwise over 35 min, and the resulting mixture stirred at 25°C for 18.5 h. After this period, the suspension was filtered, diluted with 300 mL of Et_2O, washed with 3x50 mL of 5 % KOH and 100 mL of NaOAc-saturated brine, dried over Na_2SO_4 and concentrated *in vacuo*. The product obtained in this fashion contained a little HMPA, so it was redissolved in 200 mL of Et_2O, washed with 7x50 mL of 5 % KOH and 100 mL of NaOAc-saturated brine, dried over Na_2SO_4 and the solvent removed *in vacuo* to yield (86.1 %) 29.1 g of a slightly yellowish liquid, BP 90-93°C (0.01 mm).
^1H NMR δ 7.18 (1H5', ca t, Japp=7.7), 6.99-6.85 (3H2'+4'+6', m), 5.07 (2H10', s), 4.51 (2H8', s), 3.28 (1HO-H, br.), 3.37

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(3H11', s); ^{13}C NMR δ 157.08 (C1', s), 142.63 (C3', s), 129.27 (C5', d, ^{1}J=160.8), 120.10 (C4', d, ^{1}J=163.8), 115.07 (C6', d, ^{1}J=160.8), 114.36 (C2', d, ^{1}J=157.8), 94.07 (C10', t, ^{1}J= 165.3), 64.42 (C8', t, ^{1}J=142.2), 55.54 (C11', q, ^{1}J= 141.4); IR (Neat) 3400, 3040, 2963, 2907, 1595, 1580, 1490, 1455, 1408, 1323, 1255, 1215, 1153, 1085, 1012, 1000, 931, 796, 746, 705 cm^{-1}; MS *m/e* 170 (M+2, 1.1), 169 (M+1, 12), 168 (M^{+}, 100), 152 (19.5), 151 (14.5), 139 (5), 138 (47.8), 137 (15.7), 135 (9.8), 123 (8.1), 122 (6.3), 121 (7.9), 120 (8.2), 109 (12.7), 107 (21.1), 106 (16), 105 (9.8), 95 (5.2), 91 (13), 89 (26.9), 79 (7.5), 78 (15.6), 77 (20.5), 63 (5.1), 45 (51.8).

3-(Methoxymethoxy)-1-methoxymethylbenzene (**20c'**) : Under nitrogen atmosphere, 8.8 g of a 50% NaH in oil suspension (4.4 g, 0.18 mol) was washed 4 times with hexane and suspended in 50 mL of THF. A solution of **19c'** (25 g, 0.15 mol) in 100 mL of THF was added over 50 min, and the mixture was stirred for an additional 20 min. A solution of 10.5 mL (23.3 g, 0.164 mol) of MeI in 50 mL of THF was added over 40 min. The mixture was stirred at 25°C for 1 h, carefully quenched with 50 mL of water and extracted with 4x100 mL of Et_2O. The combined organic extract was washed with 2x100 mL of 5% KOH and 100 mL of NaOAc-brine, dried over Na_2SO_4, concentrated *in vacuo* , and purified by Kugelrohr distillation (95°C, 0.35 mm) obtaining (85.6 %) 23.2 g of product as a colorless liquid, BP 62°C (0.025 mm).

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^{1}H NMR δ 7.27-7.19 (1H5', ca.t), 7.02-6.93 (3H2'+4'+6', m), 5.14 (2H10', s), 4.40 (2H8', s), 3.42 (3H11', s), 3.35 (3H9', s); ^{13}C NMR δ 157.19 (C1', s), 139.67 (C3', s), 129.19 (C5', d, ^{1}J=160.9), 120.88 (C4', d, ^{1}J=160.9), 115.30 (C2', d, ^{1}J=160.8), 115.23 (C6', d, ^{1}J=157.1), 94.20 (C10', t, ^{1}J=162.8), 74.24 (C8', t, ^{1}J=146.0), 57.83 (C11', q, ^{1}J=140.8), 55.69 (C9', ^{1}J=142.2); IR (Neat) 3060, 2960, 2920, 2845, 1595, 1345, 1460, 1450, 1390, 1330, 1263, 1220, 1163, 1110, 1092, 1038, 1005, 938, 898, 709 cm^{-1}; MS *m/e* 184 (M+2, 1.1), 183 (M+1, 10.8), 182 (M$^+$, 100), 166 (5.4), 152 (18.1), 151 (12.2), 137 (18.1), 122 (25.8), 121 (24.7), 107 (6.7), 91 (17.7), 90 (5.4), 89 (24.5), 79 (7.1), 78 (11.4), 77 (11.6), 45 (39.4).

3-Methoxymethylphenol (10c) : In a 125 mL Erlenmeyer flask 10.0 g (54.9 mmol) of 20c' were dissolved in 100 mL of MeOH and 5 mL of concentrated HCl were added. The solution was stirred at 25°C until all the starting material had disappeared by TLC (Silica gel, PhH-Me_2CO 9:1) (5.1 h), diluted with 200 mL of H_2O and extracted with 7x30 mL of CH_2Cl_2 and 1x50 mL of Et_2O. The combined organic extract was washed with 75 mL of 5 % $NaHCO_3$, dried over Na_2SO_4 and concentrated *in vacuo* obtaining (97.6 %) 7.4 g of a yellow liquid.

^{1}H NMR δ 7.83 (1HO-H, br), 7.15-7.08 (1H5', ca t), 6.83-6.69 (3H2'+4'+6', m), 4.36 (2H8', s), 3.31 (3H9', s); ^{13}C NMR δ 156.15 (C1', s), 138.84 (C3', s), 129.50 (C5', d, ^{1}J=160.4),

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119.62 (C4', d, ^1J=160.1), 114.88 (C2', d, ^1J=152.6), 114.74 (C6', d, ^1J=155.6), 74.23 (C8', t, ^1J=142.3), 57.44 (C9', q, ^1J=141.8); IR (Neat) 3300, 3050, 2940, 2880, 2830, 1600, 1595, 1490, 1460, 1390, 1285, 1233, 1200, 1165, 1083, 1011, 957, 915, 875, 797, 763, 703 cm^{-1}; MS *m/e* 140 (M+2, 0.7), 139 (M+1, 6.9), 138 (M^+, 71.7), 137 (37), 122 (6.3), 121 (19.4), 108 (39), 107 (100), 106 (24.3), 105 (6.3), 95 (25), 94 (7.1), 91 (6.3), 79 (12.7), 78 (18), 77 (42.3), 65 (7.6).

1-(Methoxymethyl)-3-[2-[2-[3-[(2-methoxyethoxy)methoxy]-phenoxy]ethoxy]ethoxy]benzene (18c) : A solution of 2.83 g (20.5 mmol) of **10c** in 25 mL of THF was added in one portion to a suspension of 1.10 g (27.5 mmol) NaOH in 20 mL HMPA, the atmosphere was purged with nitrogen, and the mixture was refluxed 15 min. A solution of 9.02 g (20.5 mmol) of **17b** in 35 mL of THF was added over 20 min. The resulting heterogeneous mixture was refluxed for 5.7 h, and cooled to 25°C. This dark suspension was filtered and the filtrate diluted with 100 mL of 5% KOH. The phases were separated and the aqueous layer was extracted with 6x30 mL of Et_2O. The combined organic layer was washed with 4x20 mL of 5% KOH and 1x50 mL of NaOAc-saturated brine, dried over Na_2SO_4, and the solvent removed *in vacuo* to yield (99.6 %) 8.32 g of a yellowish oil, BP 195-197°C (0.02 mm).

^1H NMR δ 7.23-7.07 (2H5'+5", m), 6.88-6.78 (3H2'+4'+6', m), 6.64-6.51 (3H2"+4"+6"', m), 5.18 (2H8", s), 4.36 (2H8", s), 4.09-4.02 (4H1+4, m), 3.84-3.80 (4H2+3, m), 3.76-3.72 (2H9",

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m), 3.52-3.45 (2H10", m), 3.31 (3H9', s), 3.29 (3H11", s); ^{13}C NMR δ 159.61 (C3", s), 158.63 (C1", s), 158.13 (C1', s), 139.52 (C3', s), 129.59 (C5", d, ^{1}J=159.3), 129.10 (C5', d, ^{1}J=160.8), 119.86 (C4', d, ^{1}J=159.3), 113.69 (C2', d, ^{1}J=165.2), 113.41 (C6', d, ^{1}J=154.8), 108.45 (C4", d, ^{1}J=160.8), 107.84 (C6", d, ^{1}J=162.3), 103.02 (C2", d, ^{1}J=160.8), 93.16 (C8", d, ^{1}J=166.0), 74.18 (C8', t, ^{1}J=145.0), 71.30 (C9", t, ^{1}J=141.6), 69.59 (C10", t, ^{1}J=141.9), 67.33 (C4, t, ^{1}J=150.6), 67.22 (C1, t, ^{1}J=144.2), 67.16 (C2+3, t, ^{1}J=144.1), 58.66 (C11", q, ^{1}J=141.1) 57.74 (C9', q, ^{1}J=139.8); IR (Neat) 3060, 2940, 2890, 2840, 1590, 1485, 1488, 1365, 1270, 1150, 1075, 1015, 853, 775, 698 cm^{-1}; MS *m/e* 406 (M^{+}, 0.3), 149 (6.1), 137 (6.3), 133 (13.2), 121 (10.7), 107 (7.3), 105 (9), 93 (5.8), 92 (14.6), 91 (13.7), 90 (8.4), 89 (100), 79 (9.7), 78 (7.6), 77 (12.7), 76 (5.1), 65 (5.7), 64 (6.6), 59 (86.6), 45 (10.7).

2-(Methoxymethyl)-6-[2-[2-[3-[(2-methoxyethoxy)methoxy]-2-carboxyaldehydephenoxy]ethoxy]ethoxy]benzaldehyde (3c) : Under an argon atmosphere 24.0 mL of 2.0 M (48 mmol) BuLi in hexane were diluted with 120 mL of dry hexane. The flask was cooled to 0°C in an ice-water bath and a solution of 6.5 g (16 mmol) of **18c** in 40 mL of dry benzene was added dropwise over 15 min while keeping T<10°C. The resulting suspension was kept at 10°C for 35 min, after which 9.1 mL (7.01 g, 96 mmol) of DMF were added dropwise over 10 min. The reaction mixture was stirred at 10°C for 30 min, the cooling bath was

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removed and the mixture stirred at 25°C for 1 h. The reaction was then quenched with 30 mL of 5 % KOH. The phases were separated and the aqueous layer was extracted with 10×40 mL portions of Et_2O. The combined organic extract was washed with 3×40 mL of 5% KOH and 100 mL of NaOAc-saturated brine, dried over Na_2SO_4, and concentrated *in vacuo* to yield (82.4 %) 6.1 g of product as an orange oil.
^1H NMR δ 10.62 (1H7', s), 10.50 (1H7", s), 7.50 (1H5', ca t, Japp=8.0), 7.40 (1H5", ca t, Japp=8.48), 7.29 (1H4', d, J=8.01), 6.92 (1H6', d, J=8.10), 6.83 (1H4", d, J=8.51), 6.61 (1H6", d, J=8.34), 5.34 (2H8", s), 4.80 (2H8', s), 4.27-4.15 (4H1+4, m), 4.03-3.93 (4H2+3, m), 3.87-3.82 (2H9", AA'BB'/2), 3.57-3.52 (2H10", AA'BB'/2), 3.47 (3H9', s), 3.35 (3H11", s); ^{13}C NMR δ 191.83 (C7", d, ^1J=187.6), 188.92 (C7', d, ^1J=181.7), 162.15 (C3", s), 161.12 (C1", s), 159.18 (C1', s), 142.89 (C3', s), 135.46 (C5', d, ^1J=160.5), 135.03 (C5", d, ^1J=169.4), 121.67 (C2', s), 118.90 (C4', d, ^1J=165.8), 115.96 (C2", s), 111.23 (C6', d, ^1J=171.2), 108.00 (C4", d, ^1J=173.7), 106.03 (C6", d, ^1J=162.0), 93.69 (C8", t, ^1J=167.4), 72.19 (C8', t, ^1J=145.9), 71.42 (C9", t, ^1J=139.8), 69.87 (C10", t, ^1J=143.6), 69.54 (C4, t, ^1J=143.8) 68.84 (C1, t, ^1J=145.2), 68.54 (C3, t, ^1J=145.4), 68.04 (C2, t, ^1J=141.3), 58.81 (C9', q, ^1J=144.2), 58.68 (C11", q, ^1J=137.9); IR (Neat) 3080, 2940, 2890, 2840, 2730, 1688, 1680, 1595, 1585, 1470, 1410, 1370, 1253, 1195, 1080, 1045, 967, 881, 865, 833, 792 cm^{-1}; MS *m/e* 462 (M^+, 0.2),

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373 (5.9), 342 (6.8), 193 (6.7), 177 (27.8), 165 (14.7), 163 (9.4), 161 (6.3), 159 (5.3), 151 (8.6), 149 (11.1), 147 (13.2), 137 (35.3), 135 (27.9), 134 (12.1), 131 (5.6), 121 (14.4), 119 (8.3), 108 (9.7), 107 (15), 106 (7.6), 105 (39.7), 93 (8.5), 92 (9.2), 91 (17.6), 90 (8.8), 89 (65.8), 81 (6.2), 79 (11.2), 78 (9.9), 77 (18.3), 65 (11.8), 59 (100), 45 (12.7), 43 (4.9).

6'-(2,5-Dioxahexyloxy)-2,5-dihydro-2-hydroxyisobenzofuran (21c) : Under an argon atmosphere 2.96 g (14.0 mmol) of **19c** were dissolved in 75 mL of dry benzene and cooled to 5°C. 19 mL of a 1.77 M solution of BuLi in hexane (33.6 mmol) were added dropwise over 12 min keeping T<7°C. The orange solution was stirred at 5°C for an additional 1 h. 13 mL (10.2 g, 140 mmol) of DMF were then added slowly, and the mixture stirred at 5°C for 10 min and at 15°C for 30 min. The reaction was then quenched with 25 mL of 5% KOH and the phases separated. The aqueous layer was extracted with 5x25 mL of Et_2O. The combined organic extract was washed with 3x25 of mL 5% KOH and 25 mL of NaCl-saturated 5% KOH, dried over Na_2SO_4 , and concentrated *in vacuo* to yield 1.00 g of a yellow oil which contained only starting material. The combined aqueous layer were poured into a liquid-liquid continuous extractor and extracted with Et_2O for 8 h. The organic extract was dried over Na_2SO_4, and the solvent removed in vacuo to yield (54.6 %) 1.76 g of product as the hemiacetal.

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^{1}H NMR δ 7.78 (1H5', cat, Japp=7.8), 7.03 (1H4', cad, Japp=8.1), 6.84 (1H6', cad, Japp=7.4), 6.03 (1HO-H, br.s), 5.32 (2H10', s), 5.00 (2H8', AB system, $\Delta\nu$=15.1, J=12.5), 3.85-3.80 (2H11', AA'BB'/2), 3.55-3.45 (2H12', AA'BB'/2), 3.33 (3H13', s); ^{13}C NMR δ 152.52 (C1', s), 142.60 (C3', s), 130.07 (C5', d, ^{1}J=161.1), 125.95 (C2', s), 114.13 (C4', d, ^{1}J=160.1), 113.53 (C6', d, ^{1}J=161.1), 99.16 (C7', d, ^{1}J=164.8), 93.07 (C10', t, ^{1}J=166.5), 72.67 (C8', t, ^{1}J=147.1), 71.31 (C11', t, ^{1}J=141.9), 67.42 (C12', t, ^{1}J=143.5), 58.65 (C13', q, ^{1}J=140.8).

6-[(2-Methoxyethoxy)methoxy]-2-methoxymethylbenzaldehyde (22c) : Under an argon atmosphere, 15.0 g (66.4 mmol) of 20c were dissolved in 140 mL of dry benzene, 400 mL of dry hexane were added, and the solution cooled to 10°C. Then, 60 mL of a 1.54 M solution of BuLi (92.4 mmol) in hexane were added dropwise over 10 min, keeping the temperature at 10°C. The deep red suspension was stirred at 10°C for 25 min and 20.0 mL (15.5 g, 212 mmol) of DMF were added over 10 min. The dark mixture was stirred at 10°C for 50 min and at 25°C for 3 h. It was quenched with 100 mL of 5% KOH,and the phases were separated. The aqueous layer was extracted with 7x100 mL of Et_2O. The combined organic extract was washed with 3x50 mL of 5% KOH and 1x120 mL of NaOAc-saturated brine, dried over Na_2SO_4, and concentrated *in vacuo* to yield (89.9 %) 15.2 g of a yellow liquid, which was pure by NMR. An analytical sample was further purified by PTLC (Silica gel, hexane-acetone 6:4 v/v).

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^{1}H NMR δ 10.60 (1H7', s), 7.49 (1H5', cat, Japp=8.0), 7.33 (1H4', cad, Japp=7.6), 7.17 (1H6', cad, Japp=8.3), 5.37 (2H10', s), 4.79 (2H8', br.s), 3.88-3.82 (2H11', AA'BB'/2), 3.57-3.54 (2H12', AA'BB'/2), 3.46 (3H9', s), 3.34 (3H13', s); ^{13}C NMR δ 191.06 (C7', d, ^{1}J=180.5), 160.25 (C1', s), 142.45 (C3', s), 134.48 (C5', d, ^{1}J=162.0), 120.26 (C2', s), 119.61 (C4', d, ^{1}J=164.1), 113.26 (C6', d, ^{1}J=164.4), 93.50 (C10', t, ^{1}J=167.5), 72.01 (C8', t, ^{1}J=143.4), 71.16 (C11', t, ^{1}J=139.9), 67.89 (C12', t, ^{1}J=141.9), 58.41 (C9', q, ^{1}J=140.0), 58.19 (C13', q, ^{1}J=140.5); IR (Neat) 3060, 2950, 2890, 2730, 1720, 1681, 1598, 1585, 1470, 1407, 1371, 1255, 1200, 1165, 1105, 1035, 995, 940, 855, 840, 798 cm^{-1}; MS *m/e* 254 (M^+, 0.2), 179 (4), 178 (18.9), 165 (10.8), 149 (4.9), 135 (7.4), 105 (6.1), 90 (5.5), 89 (79.4), 77 (7.5), 59 (100), 45 (8.1).

6-(Methoxymethoxy)-2-methoxymethylbenzaldehyde (22c') : Under an argon atmosphere, 5.00 g (27.5 mmol) of 20c' were dissolved in 30 mL of benzene and 90 mL of hexane and cooled down to 0°C in an ice-salt bath. Eighteen mL of a 2 M solution of BuLi in hexane (36 mmol) were added over 10 min, keeping T<3°C. The reaction mixture was stirred for 2 h at 0°C, and 8 mL (6.1 g, 82.5 mmol) of DMF were added. Stirring at 0°C was continued for 20 min, and then for 1 h at 25°C. 50 mL of 5% KOH were added, the phases were separated and the aqueous layer extracted with 7X30 mL of Et_2O. The combined organic extract was successively washed with 2X40 mL

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of 5 % KOH and 50 mL of NaOAc-saturated brine, dried over Na_2SO_4, and concentrated *in vacuo* to yield (96.6 %) 5.6 g of a yellow oil, BP 95-97°C (0.01 mm).

^1H NMR δ 10.61 (1H7', s), 7.47 (1H5', ca t, Japp=8.02), 7.33 (1H4', ca d, Japp=7.48), 7.11 (1H6', ca d, Japp=8.13), 5.24 (2H10', s), 4.79 (2H8', s), 3.47 (3H9', s), 3.44 (3H11', s); ^{13}C NMR δ 191.53 (C7', d, ^1J=181.5), 160.51 (C1', s), 142.58 (C3', s), 134.76 (C5', d, ^1J=162.3), 122.17 (C2', s), 119.71 (C4', d, ^1J=164.4), 113.26 (C6', d, ^1J=164.7), 94.57 (C10', t, ^1J=166.7), 72.07 (C8', t, ^1J=145.6), 58.48 (C9', q, ^1J=141.0), 56.18 (C11', q, ^1J=143.0); IR (Neat) 3065, 2920, 2890, 1880, 1680, 1600, 1585, 1470, 1455, 1403, 1370, 1295, 1255, 1210, 1195, 1160, 1120, 1090, 1030, 983, 933, 837, 795, 750 cm^{-1}; MS *m/e* 211 (M+1, 0.2), 210 (M^+, 1.9), 166 (5.1), 165 (37.7), 149 (7), 135 (9), 121 (4.9), 105 (12.3), 91 (6.2), 89 (5.3), 79 (4.6), 78 (6.3), 77 (13.1), 65 (5.4), 63 (5.3), 51 (7.3), 45 (100), 39 (5.4).

6-Methoxymethyl-2-hydroxybenzaldehyde (23c) :

From MEM-protected phenol : In a 500 mL Erlenmeyer flask 13.0 g (51.2 mmol) of 22c were dissolved in 275 mL of $CHCl_3$. 57.6 g (256 mmol) of anhydrous $ZnBr_2$ (Aldrich) were added, and the hetrogeneous mixture was stirred at 25°C until no starting material could be detected by TLC (Silica gel, hexane-acetone 8:2 v/v) (3.5 h). At that time 200 mL of 10% $NaHCO_3$ were added with vigorous stirring (caution, strong effervescence). The resulting suspension was fil-

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tered. The residue was washed with 2x30 mL of H_2O and 3x30 mL of $CHCl_3$. The filtrates were poured into a separatory funnel and the organic layer was separated. The aqueous layer was extracted with 3x50 mL of $CHCl_3$. The combined organic extract was dried over Na_2SO_4, concentrated *in vacuo*, and dried at 50°C (1.0 mm) to remove the methoxy ethanol byproduct, yielding (60.7 %) 5.2 g of a slightly yellowish liquid.

From MOM-protected phenol: In a 250 mL Erlenmeyer flask 4.0 g (19 mmol) of **22c'** were dissolved in 120 mL of MeOH. 2 mL of conc HCl were added, and the solution was stirred under nitrogen at 25 C. The reaction was followed by TLC (silica gel, benzene-acetone 9:1 v/v). After 8 h of stirring no starting material could be detected, so the reaction mixture was diluted with 100 mL of H_2O and extracted with 6x25 mL of CH_2Cl_2 and 6x25 mL of Et_2O. The combined organic extract was dried over Na_2SO_4 and the solvent removed *in vacuo* to yield (94.9 %) 3.0 g of a yellowish liquid, BP 80-83°C (0.075 mm).

^1H NMR δ 10.76 (1HO-H, br.s), 10.27 (1H7', s), 7.39 (1H5', dd, J_1= 8.4, J_2=7.4), 6.91 (1H6', d, J=8.4), 6.82 (1H4', d, J=7.4), 4.63 (2H8', s), 3.35 (3H9', s); ^{13}C NMR δ 195.75 (C7',s), 162.92 (C1', s), 140.90 (C3', s), 136.35 (C5',d, ^1J=159.2), 129.18 (C2', s), 120.53 (C4', d, ^1J=169.1), 118.18 (C6', d, ^1J=162.7), 71.50 (C8', t, ^1J=142.2), 57.67 (C9', q, ^1J=141.4); IR (Neat) 3020, 2960, 2920, 2860, 1645,

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1620, 1585, 1460, 1395, 1348, 1325, 1296, 1240, 1203, 1175, 1105, 1035, 995, 970, 928, 860, 815, 758, 740 cm^{-1}; MS *m/e* 168 (M+2, 5.4), 167 (M+1, 9.3), 166 (M^+, 85.6), 165 (73.2), 152 (27.4), 151 (84.2), 150 (16.3), 149 (63.4), 137 (12.3), 136 (12), 135 (42.6), 134 (100), 133 (14.5), 122 (13.2), 121 (66.2), 120 (6.5), 119 (7.5), 108 (30.8), 107 (59.4), 106 (35.7), 105 (66.6), 95 (16.4), 94 (6.3), 93 (25.2), 92 (6.1), 91 (11.8), 90 (6.9), 89 (14.7), 79 (17.6), 78 (43.3), 77 (59.9), 65 (19.9), 63 (12.2), 51 (8.2), 45 (24.1).

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BIBLIOGRAPHY.

1. Gandour, R. D. in "Transition States in Biochemical Processes"; Gandour, R. D.; Schowen, R. L. Eds; Plenum: New York, 1978, p 529.
2. Breslow, R.; Trainor, G.; Ueno, A. *J. Am. Chem. Soc.* **1983**, *105*, 2739-2744.
3. Cram, D. J.; Katz, H. E. *J. Am. Chem. Soc.* **1983**, *105*, 135-137.
4. Ihara, Y.; Nango, M.; Kimura, Y.; Kuroki, N. *J. Am. Chem. Soc.* **1983**, *105*, 1252-1255.
5. (a) Guthrie, J. P. in "Techniques of Chemistry" Vol X. Part II; Jones, J. B.; Sih, C. J.; Perlman, D. Eds.; Wiley: New York, 1976, pp 627-730. (b) Fersht, A. "Enzyme Structure and Mechanism"; W. H. Freeman: San Francisco, 1977. (c) Fife, T. H. *Adv. Phys. Org. Chem.* **1975**, *11*, 1-22.
6. Koshland, D. E. Jr. *J. Theor. Biol.* **1962**, *2*, 75-86.
7. Gandour, R. D. in Ref. 1. pp 529-552.
8. Haldane, J. B. S. "The Enzymes"; Longmans, Green and Co.: London, 1930. p 182.
9. Pauling, L. *Chem. Eng. News.* **1946**, *24*, 1375-1377.
10. Wolfenden, R. *Acc. Chem. Res.* **1972**, *5*, 10-18. Wolfenden, R. in Ref. 1, pp 555-578.
11. Lienhard, G. E. *Science*, **1973**, *180*, 149-154.
12. Schowen, R. L. in Ref. 1, pp 77-114.

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13. See for example Ref. 5b, pp 37-83. Also Walsh, C. "Enzymatic Reaction Mechanisms"; W. H. Freeman and Co.: San Francisco, 1979. pp 24-48.

14. For a recent review and a very complete compilation of effective molarities see Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183-278.

15. Bell, R. P.; Earls, D. W.; Timin, B. A. *J. Chem. Soc. Perkin 2* **1974**, 811-817.

16. Kirby, A. J.; LLoyd, G. J. *J. Chem. Soc. Perkin 2* **1976**, 1753-1761.

17. Bruice, T. C.; Pandit, U. K. *Proc. Nat. Acad. Sci. USA.* **1960**, *46*, 402-404.

18. Bruice, T. C.; Benkovic, S. J. *J. Am. Chem. Soc.* **1964**, *86*, 418-426.

19. Page, M. I. *Chem. Soc. Revs.* **1973**, *2*, 295-323. Page, M. I.; Jencks, W. P. *Proc. Nat. Acad. Sci. USA* **1971**, *68*, 1678-1683.

20. Jencks, W. P. *Adv. Enzymol.* **1975**, *43*, 219-410.

21. Bruice, T. C. *Ann. Rev. Biochem.* **1976**, *45*, 331-373.

22. De Lisi, C.; Crothers, D. M. *Biopolymers* **1973**, *12*, 1689-1709.

23. Milstein, S. ; Cohen, L. A. *J. Am. Chem. Soc.* **1972**, *94*, 9158-9165.

24. Borchardt, R. T.; Cohen, L. A. *J. Am. Chem. Soc.* **1972**, *94*, 9166-9174.

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25. Herschfield, R.; Schmir, G. L. *J. Am. Chem. Soc.* **1973**, *95*, 7359-7369. *Ibid.* **1973**, *95*, 8032-8040.

26. Karle, J. M.; Karle, I. L. *J. Am. Chem. Soc.* **1974**, *96*, 9182-9189.

27. Danforth, C.; Nicholson, J. C.; Loudon, G. M. *J. Am. Chem. Soc.* **1976**, *98*, 4275-4281.

28. Winans, R. E.; Wilcox, C. F. *J. Am. Chem. Soc.* **1976**, *98*, 4281-4285.

29. Levitt, M. in "Peptides, Polypeptides and Proteins"; Blout, E. R.; Bovey, F. A.; Goodman, M.; Lotan, N. Eds.; Wiley: New York, 1974. p 99.

30. Koshland, D. E. Jr.; Neet, K. E. *Ann. Rev. Biochem.* **1968**, *37*, 359-410. This model has been reviewed, see : Citri, N. *Adv. Enzymol.* **1973**, *37*, 397-648.

31. Storm, D. R.; Koshland, D. E. Jr. *Proc. Nat. Acad. Sci. USA* **1970**, *66*, 445-452. Koshland, D. E. Jr. *Proc. Robert A. Welch Found. Conf. Chem. Res.* **1972**, *15*, 53-91. Dafforn, G. A.; Koshland, D. E. Jr. *Bioorg. Chem.* **1971**, 129-139. Storm, D. R.; Tjian, R.; Koshland, D. E. Jr. *J. Chem. Soc. Chem. Comm.* **1971**, 854-855. Dafforn, A.; Koshland, D. E. Jr. *Proc. Nat. Acad. Sci. USA* **1971**, *68*, 2463-2467. Storm, D. R.; Koshland, D. E. Jr. *J. Am. Chem. Soc.* **1972**, *94*, 5805-5814, 5815-5825.

32. For a good historical review of the controversy surrounding the orbital steering hypothesis see ref. 7.

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33. Moriarty, R. M.; Adams, T. *J. Am. Chem. Soc.* **1973**, *95*, 4070-4071. Adams, T.; Moriarty, R. M. *Ibid.* **1973**, *95*, 4071-4073.

34. Herschfield, R.; Schmir, G. L. *J. Am. Chem. Soc.* **1972**, *94*, 6788-6793.

35. De Tar, D. F. *J. Am. Chem. Soc.* **1974**, *96*, 1254-1255, 1255-1256.

36. Page, M. I. *Biochem. Biophys. Res. Commun.* **1972**, *49*, 940-944.

37. Capon, B. *J. Chem. Soc. B.* **1971**, 1207-1209.

38. Kim, C. E.; Ingraham, L. L. *Biochim. Biophys. Acta* **1970**, *297*, 220-228.

39. Bruice, T. C.; Brown, A.; Harris, D. O. *Proc. Nat. Acad. Sci. USA* **1971**, *68*, 658-661.

40. Burgi, H. B.; Lehn, J. M.; Wipff, G. *J. Am. Chem. Soc.* **1974**, *96*, 1956-1957.

41. Scheiner, S.; Lipscomb, W. N.; Kleier, D. A. *J. Am. Chem. Soc.* **1976**, *98*, 4770-4777.

42. Umeyama, H.; Imamura, A.; Nagata, C.; Hahano, M. *J. Theor. Biol.* **1973**, *41*, 485-502.

43. Menger, F. M.; Glass, L. E. *J. Am. Chem. Soc.* **1980**, *102*, 5405-5406.

44. Menger, F. M. *Tetrahedron* **1983**, *39*, 1013-1040.

45. Deslongchamps, P. *Tetrahedron* **1975**, *31*, 2463-2490; *Heterocycles* **1977**, *7*, 1271-1317. Deslongchamps, P.; Cheriyan, U. O.; Pradere, J.-P.; Soucy, P.; Taillfeller, R. J. *Nouv. J. Chim.* **1979**, *3*, 343-350.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.

46. Deslongchamps, P. in "Stereoelectronic Effects in Organic Chemistry"; Pergamon: Oxford, 1983. pp 54-99.

47. Reference 46, pp 340-359.

48. Bender, M. L.; Kezdy, F. G.; Gunter, C. R. *J. Am. Chem. Soc.* **1964**, *86*, 3714-3721.

49. Gandour, R. D. *Bioorg. Chem.* **1981**, *10*, 169-176.

50. Hocking, W. H. *Z. Naturforsch.* **1976**, *31A*, 1113-1121. Bjarnov, E.; Hocking, W. H. *Z. Naturforsch.* **1978**, *33A*, 610-618.

51. Peterson, M. R.; Csizmadia, I. G. *J. Am. Chem. Soc.* **1979**, *101*, 1076-1079.

52. For Model A see Ref. 55. For B see Ref. 16. Model C see Arcelly, A.; Concillo, C. *J. Chem. Soc. Perkin 2* **1977**, 1753. Model D see Pollack, R. M.; Kayser, R. H.; Damewood, J. R. Jr. *J. Am. Chem. Soc.* **1977**, *99*, 8232. Models E and F can be found in Capon, B. in "Proton Transfer Reactions", Caldin, E. F.; Gold, V. Eds.; Chapman and Hall: London, 1975. pp 339-384. Model G see Kirby, A. J.; McDonald, R. S.; Smith, C. R. *J. Chem. Soc. Perkin 2* **1974**, 1495.

53. De Amaral, L.; Bastos, M. P.; Bull, H. G.; Ortiz, J. J.; Cordes, E. H. *J. Am. Chem. Soc.* **1979**, *101*, 169-173.

54. Jencks, W. P.; Carriuolo, J. *J. Am. Chem. Soc.* **1961**, *83*, 1743-1750.

55. Fersht, A. R.; Kirby, A. J. *J. Am. Chem. Soc.* **1967**, *89*, 4857-4563.

56. Kraut, J. *Ann. Rev. Biochem.* **1977**, *46*, 331-358.

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57. James, M. N. G.; Hsu, I.-N.; Delbaere, L. T. J. *Nature (London)*, **1977**, *267*, 808-813.

58. See, for instance, Kirby, A. J.; Fersht, A. R. *Progr. Bioorg. Chem.* **1971**, *1*, 1-82.

59. Fersht, A. R.; Kirby, A. J. *J. Am. Chem. Soc.* **1967**, *89*, 4853-4857.

60. Wiseman, F. L. Ph. D. Dissertation, Louisiana State University, 1982.

61. Pauling, L. in "The Nature of the Chemical Bond", 3d. Ed.; Cornell University Press, Ithaca: New York, 1960. p 239.

62. Kovach, I. M.; Elrod, J. P.; Schowen, R. L. *J. Am. Chem. Soc.* **1980**, *102*, 7530-7540.

63. Stone, A. J.; Erskine, R. W. *J. Am. Chem. Soc.* **1980**, *102*, 7185-7192.

64. This angle was not given directly in ref. 63, but it can be calculated from their data.

65. Umeyama, H. *Chem. Pharm. Bull.* **1974**, *22*, 2518-2529.

66. Gready, J. E. *Chem. Phys.* **1981**, 1-26. DelBene, J. E. *J. Chem. Phys.* **1975**, *62*, 1314-1322. Gordon, M. S.; Tallman, D. E. *Chem. Phys. Lett.* **1972**, *17*, 385-392.

67. Radom, L. *Aust. J. Chem.* **1976**, *29*, 1635-1640.

68. McMurry, J. E. *Acc. Chem. Res.* **1974**, *7*, 281-286; *Ibid.* **1983**, *16*, 405-411. McMurry, J. E.; Fleming, P.; Kees, K. L.; Krepski, L. R. *J. Org. Chem.* **1978**, *43*, 3257-3266.

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69. Mollere, P. D.; Houk, K. N.; Bomse, D. S.; Morton, T. H. *J. Am. Chem. Soc.* **1976**, *98*, 4732-4736. Lenoir, D. *Synthesis* **1977**, 553-554.

70. (a) Baumstark, A. L.; Bechara, E. J. H.; Semigran, M. J. *Tetrahedron Lett.* **1976**, 3265-3266. (b) McMurry, J. E.; Kees, K. L. *J. Org. Chem.* **1977**, *42*, 2655-2656.

71. McMurry, J. E.; Miller, D. D. *Tetrahedron Lett.* **1983**, *24*, 1885-1888. *J. Am. Chem. Soc.* **1983**, *103*, 1660-1661.

72. Parshall, G. W. *Acc. Chem. Res.* **1970**, *3*, 139-144. Bruce, M. I. *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 73-86.

73. (a) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1-360. (b) Wakefield, B. J. "The Chemistry of Organolithium Compounds"; Pergamon: New York, 1974.

74. Greene, T. W. in "Protecting Groups in Organic Synthesis"; Wiley: New York, 1981.

75. See for a recent review, Vogtle, F.; Weber, E. *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 753-776.

76. Most of the reported X-ray structures of trans stilbenes deal with acyclic compounds. See, for instance, Ruban, G.; Luger, P. *Acta Crystallogr. Sect. B* **1975**, *31B*, 2658-2662. Chesick, J. P. *Ibid.* **1973**, *29B*, 2309-2311.

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77. (a) Lerner, R. G; Dailey, B. P.; Friend, J. P. *J. Chem. Phys.* **1957**, *26*, 680-683. (b) Miyazawa, T.; Pitzer, K. S. *J. Chem. Phys.* **1959**, *30*, 1076-1086. (c) Lide, D. R. Jr. *Ann. Rev. Phys. Chem.* **1964**, *15*, 234-246. (d) Hisatune, C.; Heicklen, J. *Can. J. Spectr.* **1973**, *18*, 135-142.

78. (a) Herndon, W. C.; Feuer, J.; Hall, L. H. *Tetrahedron Lett.* **1968**, 2625-2628. (b) Leibovici, C. *J. Mol. Str.* **1971**, *10*, 333-342. (c) Kohler, H.-J.; Birnstock, F. *Z. Chem.* **1972**, *12*, 196-198. (d) Schuster, P.; Funck, T. *Chem. Phys. Lett.* **1968**, *2*, 587-588. (e) Alston, P. V.; Shillady, D. D.; Trindle, C. *J. Am. Chem. Soc.* **1975**, *97*, 469-476. (f) Gordon, M. S.; Tallman, D. E. *Chem. Phys. Lett.* **1972**, *56*, 3503-3518. (g) Gordon, M. S. *J. Mol. Str.* **1974**, *23*, 399-410. (h) Ros, P. *J. Chem. Phys.* 1968, *49*, 4902-4916. (i) Schwartz, M. E.; Hayes, E. F.; Rothenberg, S. *J. Chem. Phys.* **1970**, *52*, 2011- 2014. (j) Hopkinson, A. C.; Yates, K.; Csizmadia, I. G. *J. Chem. Phys.* **1970**, *52*, 1784-1789. (k) Allinger, N. L.; Chang, S. H. M. *Tetrahedron* **1977**, *33*, 1561-1567. (l) Radom, L.; Lathan, W. A.; Hehre, W. J.; Pople, J. A. *Aust. J. Chem.* **1972**, *25*, 1601-1612. (m) George, P.; Bock, C. W.; Schmiedekamp, A. *Chem. Phys. Lett.* **1981**, *80*, 127-130. (n) Cheney, B. V.; Christoffersen, R. E. *J. Chem. Phys.* **1972**, *56*,

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3503-3518. (o) Zirz, C.; Ahlrichs, R. *Theor. Chim. Acta* **1981**, *60*, 355-361. (p) Schafer, L.; van Alsenoy, C.; Scarsdale, J. N.; Sellers, H. L.; Pinegar, J. F. *J. Mol. Str.* **1982**, *86*, 267-275.

79. Binkley, J. S.; Whiteside, R. A.; Krishnan, R.; Seeger, R.; DeFrees, D. J.; Schlegel, H. B.; Topiol, S.; Kahn, L. R.; Pople, J. A. *QCPE* **1980**, 437

80. Hehre, E. J.; Stewart, R. F.; Pople, J. A. *J. Chem. Phys.* **1969**, *51*, 2657-2664.

81. Binkley, J. S.; Pople, J. A.; Hehre, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 939-947.

82. Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724-728.

83. The accepted convention for the basis set designation is followed here. The first basis set to be named is the one at which the energy was calculated. The basis set employed for the structure minimization is then written after the two slashes (//).

84. Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213-222.

85. For these calculations, our version of GAUSSIAN 80 had to be modified by redimensioning all the arrays that store the integrals and orbitals.

86. Curtiss, L. A.; Pople, J. A. *J. Mol. Spectroscopy* **1975**, *55*, 1-14.

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87. Williams, I. H.; Spangler, D.; Femec, D. A.; Maggiora, G. M.; Schowen, R. L. *J. Am. Chem. Soc.* **1983**, *105*, 31-40.

88. Gandour, R. D.; Hebert, L. Unpublished results.

89. Mulliken, R. S. *J. Chem. Phys.* **1955**, *23*, 1833-1840.

90. Allen, F. H.; Kennard, O.; Taylor, R. *Acc. Chem. Res.* **1983**, *16*, 146-153.

91. Newton, M. D. *J. Phys. Chem.* **1983**, *87*, 4288-4292.

92. McMurry, J. E.; Fleming, M. P. *J. Org. Chem.* **1976**, 41, 896-897.

93. McMurry, J. E.; Matz, J. R. *Tetrahedron Lett.* **1982**, *23*, 2723-2724. See also ref. 70b.

94. McMurry, J. E.; Krepski, L. R. *J. Org. Chem.* **1976**, *41*, 3929-3930.

95. Tyrlik, S.; Wolochowicz, I. *Bull. Soc. Chim. Fr.* **1973**, 2147-2148.

96. Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* **1973**, 1041-1044.

97. Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S. *J. Org. Chem.* **1976**, *41*, 260-265.

98. Pedersen, C. J. *Org. Synth.* **1972**, *52*, 66-74. Gokel, G. W.; Timko, J. M.; Cram, D. J. *J. Chem. Soc. Chem. Commun.* **1975**, 394-396. See also References 103 and 104 below.

99. Wada, F.; Arata, R.; Goto, T.; Kikukawa, T. *Bull. Chem. Soc. Japan* **1980**, *53*, 2061-2063.

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100. Kyba, E. B.; Koga, K.; Sousa, L. R.; Siegel, M. G.; Cram, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 2692-2693.

101. Jaunin, R.; Magnenat, J.-P. *Helv. Chim. Acta* **1959**, *42*, 328-334.

102. Greber, G. V. *Makromol. Chem.* **1956**, *17*, 154-157.

103. Greber, G. V.; Oschmann, W. *Makromol. Chem.* **1961**, *44-46*, 328-334.

104. Vogtle, F.; Heimann, U. *Chem. Ber.* **1978**, *111*, 2757-2764. Vogtle, F.; Wester, N. *Ibid.* **1979**, *112*, 3723-3727.

105. Tirado-Rives, J.; Gandour, R. D.; Fronczek, F. R. *Tetrahedron Lett.* **1982**, *23*, 1639-1642.

106. Tirado-Rives, J.; Oliver, M. A.; Fronczek, F. R.; Gandour, R. D. *J. Org. Chem.* **1984**, *49*, 1627-1634.

107. Jackman, L. M.; Sternhill, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd. ed.; Pergammon, Oxford, 1969; p. 224.

108. Berenstein, J. *Acta Crystallogr. Sect. B.* **1975**, *B31*, 1268-1271.

109. Fronckzeck, F. R.; Oliver, M. A.; Gandour, R. D. *Acta Crystallogr. Sect. C.* **1984**, *C40*, 504-506.

110. Norrestan, R.; Hovmoller, S.; Palm, T.-B.; Gothe, R.; Wachmeister, C. A. *Acta Crystallogr. Sect. B.* **1977**, *B33*, 370-376.

111. This material was prepared in our laboratories by a modification of the published methods. Kyba, E. P.;

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Helgeson, R. C.; Madan, K.; Gokel, G. W.; Tarnowski, T. L.; Moore, S. S.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 2564-2571. In our modification, methylene chloride was added to the reaction mixture and it was kept at 0°C for 24 hrs.

112. This compound was prepared previously[103] and recrystallized from from aqueous methanol. However, the molecular weight these authors obtained by melting point depression of naphthalene was 298 g/mol instead of the expected 314.3. When the compound prepared here was recrystallized in this same mixture of solvents, a MP of 67.5-68°C was obtained.

113. The author would like to acknowledge the donation of a generous amount of this material by Dr. George W. Gokel.

114. Kopp, P. *Liebigs Ann. Chem.* **1893**, *277*, 339-361.

115. Parham, W. E.; Anderson, E. L. *J. Am. Chem. Soc.* **1948**, *70*, 4187-4189.

116. Stern, R.; English, J.; Cassidy, H. G. *J. Am. Chem. Soc.* **1957**, *79*, 5792-5797. Christensen, H. *Synthetic Comm.* **1975**, *5*, 65-78. Townsend, C. A.; Bloom, L. M. *Tetrahedron Lett.* **1981**, *22*, 3923-4.

117. Meyers, A. I.; Mihelich, E. D. *J. Org. Chem.* **1975**, *40*, 3158-3159.

118. An example of the use of esters in ortho lithiations can be found in Upton, C. J.; Beak, P. *J. Org. Chem.*

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1975, 40, 1094-1098. For some examples on the use of amides see Beak, P.; Brubaker, G. R.; Farney, *J. Am. Chem. Soc.* 1976, *98*, 3621-3627. Beak, P.; Brown, R. *J. Org. Chem.* 1977, *42*, 1823-1824.

119. Two consecutive reactions are required to convert a carboxylic acid into an oxazoline, and two different hydrolysis steps are used for the reverse. See, for instance, Meyers, A. I.; Temple, D. L.; Haidukewych, D.; Mihelich, E. D. *J. Org. Chem.* 1974, *39*, 2787-2793.

120. Plaumann, H. P.; Keay, B. A.; Rodrigo, R. *Tetrahedron Lett.* 1976, 4921-4924.

121. For some examples of this reaction see Corey, E. J.; Achiwa, K. *Tetrahedron Lett.* 1969, 1837-1839. Shamma, M.; Rodriguez, H. R. *Tetrahedron*, 1968, *24*, 6583-6589.

122. Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* 1968, *90*, 5616-5617.

123. Fischer, E.; Giebe, G. *Berichte* 1898, *30*, 3053-3054.

124. Winkle, M. R.; Ronald, R. C. *J. Org. Chem.* 1982, *47*, 2101-2108.

125. Nickles, E. F. *J. Agr. Food. Chem.* 1969, *17*, 939-953.

126. Kantlehner, W.; Gutbrod, H.-D.; Grob, P. *Liebig's Ann. Chem.* 1979, 522-527. Kantlehner, W.; Gutbrod, H.-D. *Ibid.* 1979, 1362-1369.

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127. Bredereck, H.; Effenberger, F.; Simchen, G. *Chem. Ber.* **1936**, *96*, 1350-1355.

128. Rausch, M. D.; Ciapenelli, D. J. *J. Organomet. Chem.* **1967**, *10*, 127-136.

129. Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809-812.

130. Several reagents have been shown to be useful for the hydrolysis of methyl ethers. See Hanessian, S.; Guindon, Y. *Tetrahedron Lett.* **1980**, *21*, 2305-2308. Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761-3763. Bhatt, M. V. *J. Organomet. Chem.* **1978**, *156*, 221-226. However, most of the selectivities reported are not adequate for the compounds used in this work. While all of these reagents will cleave aryl-methyl in preference to other aryl-alkyl ethers, they will react considerably faster with dialkyl ethers.

131. Reese, C. B.; Saffhill, R.; Sulston, J. E. *J. Am. Chem. Soc.* **1967**, *89*, 3366-3368.

132. Meyer, N.; Seebach, D. *Chem. Ber.* **1980**, *113*, 1304-1319. *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 521-522.

133. (a) Schmidt, H.-J.; Schafer, H. J.; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 68-69, 69-70. (b) Olah, G. A.; Welch, J.; Ho, T.-L. *J. Am. Chem. Soc.* **1976**, *98*, 6717-6718. (c) Lovins, R. E.; Andrews, L. J.; Keefer,

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R. M. *J. Org. Chem.* **1965**, *30*, 4150-4154. (d) Cooper, T. A.; Waters, W. A. *J. Chem. Soc. B* **1965**, 455-463. (e) Juenge, E. C.; Corey, M. D.; Beal, D. A. *Tetrahedron* **1971**, *27*, 2761-2764. Juenge, E. C.; Beal, D. A. *Tetrahedron Lett.* **1968**, 5819-5820.

134. Tirado-Rives, J.; Gandour, R. D. *Org. Prep. Proc. Int.* in press.

135. The preparation of butyllithium in pentane is described in Bryce-Smith, D.; Turner, E. E. *J. Chem. Soc.* 1953, 861-867. The same procedure was used except for the use of hexane as solvent.

136. Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* 1967, *9*, 165-168.

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Appendix 1. Complete Z-Matrices and List of Variables for the Formic Acid Pentahydrate Conformers.

Structures optimized at the 4-31G level.

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Syn Formic Acid Pentahydrate. 4-31G Optimized Structure.

H1						
C1	1	C1H2				
O1	2	O1C1	1	O1C1H1		
H2	3	H201	2	H201C1	1	H201C1
O3	3	O301	2	H201C1	1	H201C1
O2	2	O2C1	3	O2C101	4	O2C101
H31	5	H3103	3	H310301	2	H310201
H32	5	H3203	3	H320301	2	H320301
H41	6	H4102	2	H4102C1	4	H4102C1
O4	6	O402	2	H4102C1	4	H4102C1
H42	10	H4204	9	H4204H41	4	H4204H41
H51	6	H5102	2	H5102C1	1	H5102C1
O5	6	O502	2	H5102C1	1	H5102C1
H52	13	H5205	12	H5205H51	1	H5205H51
H61	3	H6101	2	H6101C1	6	H6101C1
O6	3	O601	2	H6101C1	6	H6101C1
H62	16	H6206	15	H6206H61	4	H6206H61
H71	3	H7101	2	H7101C1	6	H7101C1
O7	3	O701	2	H7101C1	6	H7101C1
H72	19	H7207	18	H7207H71	4	H7207H71

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Bond Lengths(Å)		Bond Angles(°)		Dihedrals(°)	
C1H2	= 1.0729	01C1H1	= 112.6137	H201C1H1	= 182.5524
01C1	= 1.3169	H201C1	= 119.6818	02C101H2	= 3.0542
H201	= 1.0126	02C101	= 124.9409	H310201C1	= -8.9113
0301	= 2.5280	H310301	= 116.1994	H320301C1	= -213.9018
02C1	= 1.2159	H320301	= 124.6096	H4102C1H2	= 2.7157
H3103	= 0.9702	H4102C1	= 122.0868	H4204H41H2	= 177.1290
H3203	= 0.9485	H4204H41	= 111.4945	H5102C1H1	= -18.9020
H4102	= 1.9098	H5102C1	= 174.4937	H5205H51H1	= 32.0127
0402C	= 2.8648	H5205H51	= 111.8205	H6101C102	= 118.5145
H4204	= 0.9512	H6101C1	= 132.0483	H6206H61H2	= -132.1136
H5102	= 1.9836	H6206H61	= 108.9035	H7101C102	= -165.7824
0502	= 2.9352	H7101C1	= 120.4515	H7207H71H2	= 303.7463
H5205	= 0.9490	H7207H71	= 111.9150		
H6101	= 2.2524				
0601	= 3.2015				
H6206	= 0.9523				
H7101	= 1.9900				
0701A	= 2.9430				
H7207	= 0.9497				

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Anti Formic Acid Pentahydrate. 4-31G Optimized Structure.

H1						
C1	1	C1H2				
O1	2	O1C1	1	O1C1H1		
H2	3	H201	2	H201C1	1	H201C1H1
O3	3	O301	2	H201C1	1	H201C1H1
O2	2	O2C1	3	O2C101	4	O2C101H2
H31	5	H3103	3	H310301	2	H310201C1
H32	5	H3203	3	H320301	2	H320301C1
H41	6	H4102	2	H4102C1	4	H4102C1H2
O4	6	O402	2	H4102C1	4	H4102C1H2
H42	10	H4204	9	H4204H41	4	H4204H41H1
H51	6	H5102	2	H5102C1	1	H5102C1H1
O5	6	O502	2	H5102C1	1	H5102C1H1
H52	13	H5205	12	H5205H51	1	H5205H51H1
H61	3	H6101	2	H6101C1	1	H6101C1H1
O6	3	O601	2	H6101C1	1	H6101C1H1
H62	16	H6206	15	H6201H61	4	H6206H61H2
H71	3	H7101	2	H7101C1	1	H7101C1H1
O7	3	O701	2	H7101C1	1	H7101C1H1
H72	19	H7207	18	H7207H71	4	H7207H71H2

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Bond Lengths(Å)		Bond Angles(°)		Dihedrals(°)	
C1H2	= 1.0769	O1C1H1	= 115.6640	H201C1H1	= -1.4037
O1C1	= 1.3265	H201C1	= 118.5090	O2C101H2	= 178.5663
H201	= 0.9809	O2C101	= 121.9688	H310201C1	= 93.5402
0301	= 2.5956	H310301	= 123.6027	H320301C1	= -106.9222
O2C1	= 1.2065	H320301	= 121.1138	H4102C1H2	= -5.8704
H3103	= 0.9510	H4102C1	= 119.6624	H4204H41H1	= 66.4787
H3203	= 0.9513	H4204H41	= 109.6250	H5102C1H1	= -0.5690
H4102	= 2.0214	H5102C1	= 124.0225	H5205H51H1	= 175.5811
0402	= 2.9765	H5205H51	= 111.0819	H6101C1H1	= 149.7353
H4204	= 0.9535	H6101C1	= 119.9557	H6201H61H2	= -74.5247
H5102	= 1.9925	H6206H61	= 109.4072	H7101C1H1	= -140.8407
0502	= 2.9460	H7101C1	= 118.1383	H7207H71H2	= 182.5725
H5205	= 0.9497	H7207H71	= 108.1608		
H6101	= 2.1556				
0601	= 3.1058				
H6206	= 0.9527				
H7101	= 2.1556				
0701	= 3.1058				
H7207	= 0.9563				

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Appendix 2. Crystallographic Data for Stilbene Cycles.

Summary of Crystal Data for Stilbene Cycles.

Compound	*E*- 7h	*Z*- 7h	*Z*- 7m	*E*- 8h	*E*- 9h
Formula	$C_{16}H_{12}O_2$	$C_{16}H_{12}O_2$	$C_{22}H_{22}O_2$	$C_{16}H_{22}O_2$	$C_{14}H_{12}O_2$
Formula Weight	282.3	282.3	310.4	280.4	212.3
Crystal System	Orthorombic	Monoclinic	Orthorombic	Orthorombic	Orthorombic
Space Group	Pbca	$P2_1$	$P2_12_12_1$	Pbca	Pbca
a(A)	21.914(4)	7.609(3)	11.510(3)	22.369(4)	18.591(4)
b(A)	18.720(4)	7.956(4)	18.511(5)	19.107(3)	11.392(7)
c(A)	7.164(1)	12.614(4)	7.877(4)	7.211(1)	5.098(1)
β(°)	—	99.98(3)	—	—	—
Z	8	2	4	8	4
Density(g cm^{-3})	1.276	1.247	1.228	1.208	1.306
μ (cm^{-1})	7.02	0.78	0.76	0.72	0.81
θ limits (°)	2 ≤θ≤70	1≤θ≤27	1≤θ≤28	1≤θ≤20	1≤θ≤25
Unique Data	2784	2140	2316	1441	944
Observed Data	1841	1344	1344	751	514
Variables	263	189	209	85	97
R	0.041	0.050	0.042	0.069	0.044
Rw	0.059	0.061	0.055	0.066	0.048
Residual (eA^{-3})	0.22	0.21	0.18	0.29	0.15
Refinement Type	Anisotropic Isotropic H	Anisotropic	Anisotropic	Isotropic	Anisotropic Isotopic H

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Table A2.1 Coordinates for *E* 7h.

ATOM	X	Y	Z
O1	0.90126(5)	0.46176(6)	0.6188(2)
O2	0.82307(6)	0.49761(7)	0.9357(2)
O3	0.73960(6)	0.39181(7)	0.8729(2)
C1	0.69865(7	0.33032(8	0.6175(2)
C2	0.68853(8	0.36698(9	0.7866(3)
C3	0.63010(9	0.37451(10	0.8581(3)
C4	0.58135(8	0.34282(10	0.7677(3)
C5	0.59014(8	0.30407(10	0.6076(3)
C6	0.64823(8	0.29883(9	0.5334(2)
C7	0.75861(8	0.32322(8	0.5270(2)
C8	0.80873(8	0.36109(8	0.5578(2)
C9	0.86695(8	0.35577(8	0.4594(2)
C10	0.88067(8	0.30282(9	0.3267(2)
C11	0.93561(8	0.30121(10	0.2354(3)
C12	0.97928(8	0.35190(11	0.2716(3)
C13	0.96759(8	0.40488(10	0.4015(2)
C14	0.91244(7	0.40633(8	0.4944(2)
C15	0.91680(8	0.44626(10	0.8095(3)
C16	0.88736(10	0.50242(12	0.9307(3)
C17	0.80028(10	0.45316(11	1.0808(3)
C18	0.73635(9	0.43265(10	1.0398(2)

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Table A2.2 Coordinates of Hydrogen Atoms, *E* 7h.

Atom	x	y	z
H3	0.6202	0.4008	0.9815
H4	0.5433	0.3510	0.8169
H5	0.5546	0.2824	0.5488
H6	0.6561	0.2695	0.4109
H7	0.7591	0.2868	0.4275
H8	0.8090	0.3963	0.6507
H10	0.8529	0.2670	0.3037
H11	0.9433	0.2631	0.1483
H12	1.0184	0.3528	0.2112
H13	1.0015	0.4406	0.4303
H151	0.9613	0.4452	0.8279
H152	0.9605	0.3994	0.8431
H161	0.8977	0.5508	0.8830
H162	0.9050	0.5001	1.0546
H171	0.8027	0.4730	1.2055
H172	0.8295	0.4140	1.0668
H181	0.7117	0.4732	1.0167
H182	0.7209	0.4009	1.1380

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Table A2.3 Coordinates for Z 7h.

Atom	x	y	z
O1	0.0928(2)	0.2578	0.3710(2)
O2	0.2760(2)	0.5920(3)	0.4028(2)
O3	-0.0568(2)	0.7496(3)	0.3212(1)
C1	-0.3499(3)	0.6966(4)	0.2377(2)
C2	-0.2039(3)	0.8061(4)	0.2512(2)
C3	-0.2146(4)	0.9597(4)	0.2011(2)
C4	-0.3727(5)	1.0113(5)	0.1384(3)
C5	-0.5193(4)	0.9085(6)	0.1267(3)
C6	-0.5079(4)	0.7547(5)	0.1756(3)
C7	-0.3448(3)	0.5303(5)	0.2881(2)
C8	-0.2288(4)	0.4072(4)	0.2858(2)
C9	-0.0802(3)	0.4017(4)	0.2249(2)
C10	-0.0961(4)	0.4648(5)	0.1204(2)
C11	0.0377(5)	0.4458(6)	0.0615(2)
C12	0.1929(4)	0.3615(5)	0.1046(3)
C13	0.2133(4)	0.3009(4)	0.2078(3)
C14	0.0796(3)	0.3216(4)	0.2677(2)
C15	0.2431(4)	0.3097(5)	0.4491(3)
C16	0.2325(4)	0.4849(6)	0.4818(3)
C17	0.2382(4)	0.7632(5)	0.4142(3)
C18	0.1096(3)	0.8314(5)	0.3217(3)

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Table A2.4 Coordinates of Hydrogen Atoms, *Z* 7h.

Atom	x	y	z
H3	-0.1129	1.0309	0.2095
H4	-0.3796	1.1176	0.1036
H5	-0.6287	0.9440	0.0845
H6	-0.6108	0.6851	0.1671
H7	-0.4375	0.5076	0.3278
H8	-0.2415	0.3113	0.3285
H10	-0.2021	0.5221	0.0895
H11	0.0241	0.4907	-0.0093
H12	0.2844	0.3456	0.0631
H13	0.3202	0.2444	0.2382
H151	0.2494	0.2405	0.5110
H152	0.3483	0.2955	0.4190
H161	0.3137	0.5031	0.5470
H162	0.1146	0.5086	0.4927
H171	0.1889	0.7766	0.4780
H172	0.3464	0.8250	0.4206
H181	0.1511	0.8093	0.2562
H182	0.0964	0.9492	0.3298

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Table A2.5 Coordinates for Z 7m.

Atom	x	y	z
O1	0.9340(2)	0.0336(1)	0.8231(3)
O2	0.6915(2)	0.0402(1)	0.7934(3)
O3	0.7245(2)	0.1848(1)	0.8911(3)
C1	0.9219(2)	0.2174(1)	0.8988(4)
C2	0.8141(3)	0.2206(2)	0.8159(4)
C3	0.8017(3)	0.2618(2)	0.6697(4)
C4	0.8964(4)	0.3013(2)	0.6081(4)
C5	1.0016(3)	0.2974(2)	0.6865(4)
C6	1.0137(3)	0.2560(2)	0.8307(4)
C7	0.9360(2)	0.1769(1)	1.0636(3)
C8	1.0156(2)	0.1253(1)	1.0820(3)
C9	1.0896(2)	0.0984(1)	0.9396(3)
C10	1.2079(2)	0.1158(1)	0.9375(4)
C11	1.2798(3)	0.0936(2)	0.8082(5)
C12	1.2358(3)	0.0520(2)	0.6782(4)
C13	1.1204(3)	0.0326(2)	0.6793(4)
C14	1.0479(3)	0.0542(1)	0.8108(4)
C15	0.8817(3)	0.0039(2)	0.6769(4)
C16	0.7578(3)	-0.0161(2)	0.7181(4)
C17	0.6635(3)	0.0974(2)	0.6832(4)
C18	0.6292(3)	0.1607(2)	0.7908(5)
C19	0.8609(3)	0.2039(2)	1.2068(4)
C20	1.0393(3)	0.0889(2)	1.2495(4)

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Table A2.6 Coordinates of Hydrogen Atoms, Z 7m.

Atom	x	y	z
H3	0.7293	0.2632	0.6119
H4	0.8872	0.3310	0.5108
H5	1.0663	0.3231	0.6420
H6	1.0873	0.2539	0.8851
H10	1.2394	0.1437	1.0278
H11	1.3595	0.1069	0.8085
H12	1.2849	0.0368	0.5882
H13	1.0980	0.0041	0.5893
H151	0.8827	0.0384	0.5877
H152	0.9232	-0.0380	0.6426
H161	0.7590	-0.0558	0.7944
H162	0.7205	-0.0300	0.6157
H171	0.7290	0.1094	0.6155
H172	0.6007	0.0837	0.6118
H181	0.5670	0.1470	0.8625
H182	0.6047	0.1990	0.7181
H191	0.8325	0.2495	1.1709
H192	0.9054	0.2088	1.3077
H193	0.7982	0.1715	1.2265
H201	0.9707	0.0996	1.3320
H202	1.1095	0.1071	1.2962
H203	1.0460	0.0382	1.2328
H102	0.7371	0.0604	0.8905
H202	0.6174	0.0189	0.8368

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Table A2.7 Coordinates for *E* 8h.

Atom	x	y	z
O1	0.4144(2)	0.0475(3)	0.8745(8)
O2	0.2543(3)	0.1062(3)	0.6384(8)
C1	0.2153(3)	0.1716(4)	0.883(1)
C2	0.2048(4)	0.1336(4)	0.718(1)
C3	0.1477(4)	0.1255(4)	0.646(1)
C4	0.1011(4)	0.1580(4)	0.735(1)
C5	0.1087(4)	0.1969(4)	0.891(1)
C6	0.1659(4)	0.2035(4)	0.962(1)
C7	0.2738(3)	0.1795(4)	0.970(1)
C8	0.3230(3)	0.1435(4)	0.944(1)
C9	0.3799(3)	0.1492(4)	1.039(1)
C10	0.3933(4)	0.2015(4)	1.171(1)
C11	0.4486(4)	0.2040(4)	1.257(1)
C12	0.4920(4)	0.1558(4)	1.217(1)
C13	0.4801(4)	0.1029(4)	1.088(1)
C14	0.4255(3)	0.1018(4)	1.002(1)
C15	0.4323(4)	0.0634(4)	0.687(1)
C16	0.4112(5)	0.0051(5)	0.561(2)
C17	0.3439(4)	-0.0004(5)	0.549(1)
C18	0.3150(4)	0.0514(5)	0.419(1)
C19	0.2519(4)	0.0694(5)	0.458(1)

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Table A2.8 Coordinates of Hydrogen Atoms, *E* 8h.

Atom	x	y	z
H3	0.1410	0.0980	0.5383
H4	0.0620	0.1533	0.6848
H5	0.0756	0.2189	0.9496
H6	0.1716	0.2311	1.0705
H7	0.2767	0.2160	1.0593
H8	0.3211	0.1089	0.8497
H10	0.3639	0.2355	1.2012
H11	0.4566	0.2397	1.3453
H12	0.5299	0.1503	1.2756
H13	0.5094	0.0695	1.0590
H151	0.4746	0.0670	0.6806
H152	0.4148	0.1064	0.6490
H161	0.4264	-0.0379	0.6075
H162	0.4266	0.0132	0.4404
H171	0.3279	0.0067	0.6694
H172	0.3342	-0.0462	0.5074
H181	0.3168	0.0325	0.2976
H182	0.3376	0.0935	0.4241
H191	0.2281	0.0283	0.4672
H192	0.2362	0.0090	0.3646

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Table A2.9 Coordinates for *E* 9h.

Atom	x	y	z
O1	0.0645(1)	0.1961(1)	0.5484(4)
C1	0.0977(1)	0.0873(2)	0.5481(5)
C2	0.0720(1)	0.0041(2)	0.7262(5)
C3	0.1068(1)	-0.1053(2)	0.7300(6)
C4	0.1637(2)	-0.1296(2)	0.5642(6)
C5	0.1871(2)	-0.0451(3)	0.3890(6)
C6	0.1546(2)	0.0628(2)	0.3825(5)
C7	0.0097(1)	0.0301(2)	0.8942(5)
H3	0.088(1)	-0.166(2)	0.858(5)
H4	0.187(1)	-0.210(2)	0.574(5)
H5	0.226(1)	-0.064(2)	0.270(6)
H6	0.169(1)	0.120(2)	0.248(5)
H7	-0.018(1)	0.097(2)	0.834(5)
H10	0.064(2)	0.231(3)	0.391(7)

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Appendix 3. Other Synthetic Routes to Model 1.

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The low-valent titanium reaction of dialdehydes was chosen for the formation of the stilbenic cycle in the model 1 because it seemed to be the most efficient and straightforward preparation. The preference of this procedure for intramolecular rather than intermolecular reaction, its insensitivity to steric hindrance, and the symmetry in the precursor dialdehyde made it extremely attractive as a synthetic method. In addition, the reactions conducted on simpler models (described in Chapter III of this dissertation) with moderate yields were very encouraging, and seemed to indicate the potential applicability of this reaction in the synthesis of the functionalized stilbene cycle 1.

When the titanium induced cyclization was tried with the various functionalized dialdehyde precursors to generate 1, no evidence of cyclization could be found. This route was, therefore, not applicable for the synthesis of the desired model, at least in my hands. Still, a large number of potentially useful intermediates was generated in the course of this research, and several alternative synthetic routes to the model 1 could be based on these intermediates.

The purpose of this appendix is to illustrate some of the most promising synthetic routes which can be used to prepare the desired stilbene cycle by using these intermediates. These alternative pathways to stilbenes are described in ascending order of required modifications of the interme-

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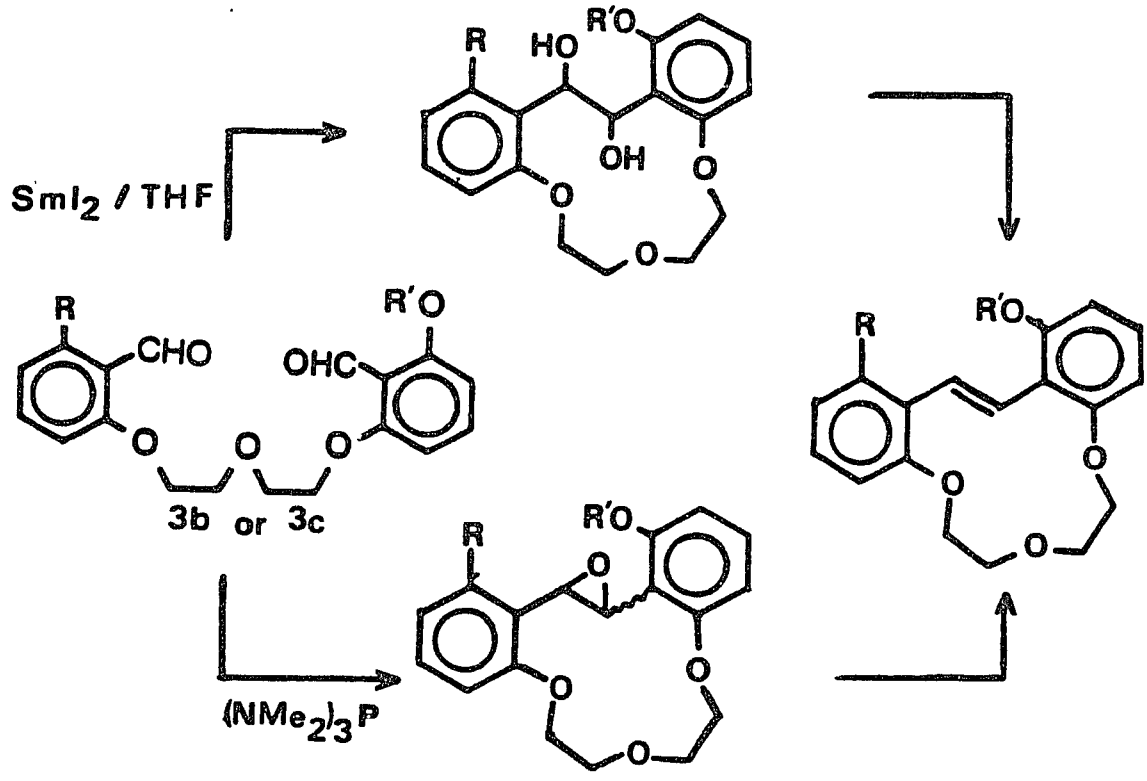
diates available. That is, the reactions described first use the compounds already prepared, while those requiring additional modifications to these intermediates are listed later.

The bis(benzaldehyde)ethers **3b** and **3c**, generated by dilithiation, can be cyclized to a pinacol by use of samarium diiodide. This reaction is known to be compatible with unsaturated or acidic functionalities.[1] The resulting pinacol can be then converted to the alkene by the procedure of Eastwood et al.[2] Alternatively, treatment of this diol with phosphorus tribromide and cuprous bromide followed by zinc



In a parallel manner, the reaction of dialdehydes with hexamethylphosphoroustriamide (HMPT) leads to oxiranes.[4] The

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oxirane products, depending on the stereochemistry, can be deoxygenated to the corresponding alkenes stereoselectively by use of lithium phenyldimethylsilane[5] or potassium cyanoselenide[6], or to the thermodynamically most stable isomer by treatment with zinc-copper couple.[7]

These two reactions use the same intermediate dialdehyde as in the titanium reaction. In addition, they can be done in an intramolecular fashion in the already formed diether. This would alleviate the problem shared by the latter alternative approaches, in which an acyclic stilbene is initially formed and then bridged in a subsequent step.

Most of the remaining procedures generate a C-C bond through the use of alkyl halides. These derivatives can be easily obtained from any aldehyde synthesized before by means of a $NaBH_4$ reduction to a benzylic alcohol followed by a tosylation and a Finkelstein reaction to give a halide. This route, although one-step longer than the direct treatment of the benzyl alcohol with thionyl chloride or phosphorus bromide, is milder and safer for the various acid-sensitive protecting groups used in the course of this work.

$$ArCHO \xrightarrow{NaBH_4} ArCH_2OH \xrightarrow[Py]{TsCl} ArCH_2OTs \xrightarrow{NaI} ArCH_2I$$

Once these various halides are obtained, the most convenient way to form a stilbene is through the initial formation of an unsymmetric thioether. Sulfur extrusion *via* the Stevens rearrengement leads to the diarylethane,[8] which can

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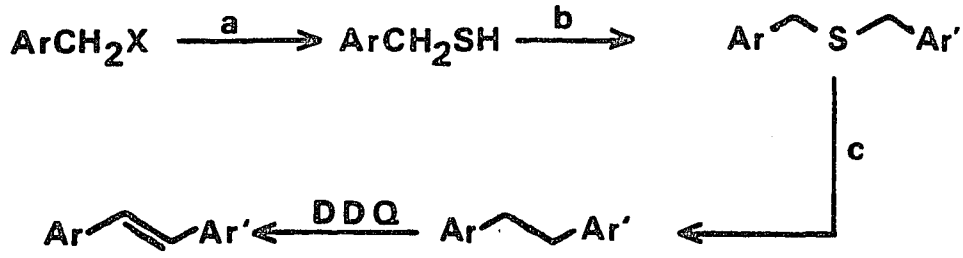
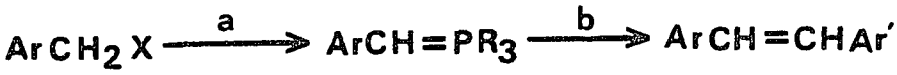
be dehydrogenated by treatment with DDQ (dichlorodicyanoquinone).[9]

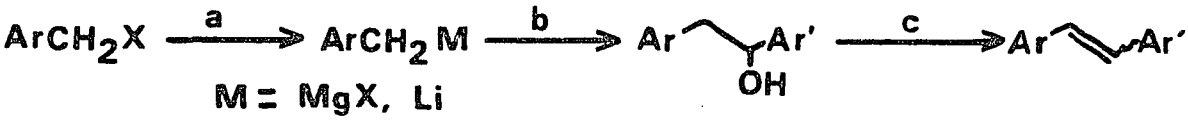


(a) 1. $(H_2N)_2CS$. 2. aq. KOH. (b) $Ar'CH_2X$-KOH/EtOH. (c) 1. $(MeO)_2CHBF_4$. 2. t-BuOK

Having both halides and aldehydes, the former can be used to prepare phosphorus ylides *via* a Wittig reaction to form directly a stilbene. Alternatively, Grignards or organolithiums reagents can be prepared, reacted with the aldehydes and the intermediate alcohols dehydrated to form the double bond.



(a) 1. PR_3. 2. BuLi. (b) Ar'CHO



(a) Mg/Et_2O or BuLi. (b) Ar'CHO. (c) H_3O^+

Another alternative routes, partially explored in these laboratories,[10] are the initial formation of a carbon-carbon triple bond (diarylethyne) *via* a Castro-Stephens coupling of a copper(I) ethynide with an aryl iodide.[11] The resulting

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acetylene can be hydrogenated to a stilbene by reduction with aqueous chromous sulfate.[12]

(a) Py, reflux. (b) Aq. $CrSO_4$

The necessary aryl iodide can be prepared by lithiation, presumably under the same conditions developed for the synthesis of the corresponding aldehyde, followed by reaction with iodine. The copper ethynide can be prepared from the previously synthesized aldehyde by known procedures.[13]

(a) $LiC(Cl)_2P(O)(OEt)_2$. (b) 1. 2BuLi. 2. H_2O. (c) $CuSO_4$-NH_2OH/H_2O

This last synthetic route suffers of the same problem as the Wittig, Grignard, or lithium-halogen exchange. Namely, an acyclic stilbene is formed. This intermediate still needs to be formed into a cyclic ether. The first two synthetic methods, HMPT-promoted formation of an epoxide and SmI_2 reduction to a pinacol, are therefore to be preferred over other routes as alternatives to the low-valent titanium cyclization.

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References Cited.

1. Souppe, J.; Danon, L.; Namy, J. L.; Kagan, H. B. *J. Organomet. Chem.* **1983**, *250*, 227-236.
2. Eastwood, F. W.; Harrington, K. J.; Josan, J. S.; Pura, J. L. *Tetrahedron Lett.* **1970**, 5223-5224.
3. Tanaka, S.; Yasuda, A.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1975**, *97*, 3252-3254.
4. Newman, M. S.; Blum, S. *J. Am. Chem. Soc.* **1964**, *86*, 5598-5600. Mark, D. *Ibid.* **1963**, *85*, 1884-1885.
5. Reetz, M. T.; Plachky, M. *Synthesis* **1976**, 199-200.
6. Behan, J. M.; Johnstone, R. A. W.; Wright, M. J. *J. Chem. Soc. Perkin I* **1975**, 1216-1217.
7. Kupchan, S. M.; Maruyama, M. *J. Org. Chem.* **1971**, *36*, 1187-1191.
8. Mitchell, R. H.; Lai, Y.-H. *J. Org. Chem.* **1984**, *49*, 2534-2540.
9. Fu, P. D.; Lee, H.-M.; Harvey, R. G. *Tetrahedron Lett.* **1978**, 551-554.
10. Oliver, M. A.; Gandour, R. D. Unpublished results.
11. Castro, C. E.; Stephens, R. D. *J. Org. Chem.* **1963**, *28*, 3313-3315.
12. Stephens, R. D.; Castro, C. E. *J. Am. Chem. Soc.* **1964**, *3313-3315*.
13. *Villieras, J.; Perriot, P.; Normant, J. F. Synthesis* **1975**, 458-461.

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VITA.

Julian Tirado-Rives was born in Guaymas, Sonora, Mexico in january 9, 1957. He attended the Unidad Guaymas of Instituto Tecnologico y de Estudios Superiores de Monterrey, where he finished his High School education in 1973. Afterwards, he went to Monterrey, Nuevo Leon, where he obtained the degree of Licenciado en Ciencias Quimicas (the equivalent of an american B. S. in Chemistry) from the Instituto Tecnologico y de Estudios Superiores de Monterrey in 1977. After finishing college he worked for Pigmentos y Oxidos, S. A. in Monterrey from 1977 to 1979 as a Research Chemist. In December of 1979 he married the former Patricia Morales and came to Louisiana State University to further pursue his education. While at LSU, his son, Jesus Alejandro Tirado, was born in November 6,1981. Julian Tirado-Rives is presently a candidate to the degree of Doctor in Philosophy at the Department of Chemistry.

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EXAMINATION AND THESIS REPORT

Candidate: Julian Tirado-Rives

Major Field: Organic Chemistry

Title of Thesis: Stereoelectronic Effects in General Base Catalysis by Carboxylate. Theoretical Calculations and Studies in the Synthesis of New Intramolecular Models of Enzymatic Catalysis

Approved:

Richard D. Gandour
Major Professor and Chairman

William Regan
Dean of the Graduate School

EXAMINING COMMITTEE:

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Date of Examination:

December 3, 1984

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